

A National Assessment of Methadone-Associated Mortality: Background Briefing Report



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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 – for a National Assessment of Methadone-Associated Mortality in May 2003. In preparation for the National Assessment, SAMHSA commissioned this Background Briefing Report, which contains research data and other information to help establish a common understanding of the problem. The Briefing Report was distributed to participants in advance of the May meeting.

Participants in the National Assessment carefully reviewed the information presented in this Background Briefing Report, as well as data presented at the meeting on methadone formulations, distribution, patterns of prescribing and dispensing, as well as the relevant data on drug toxicology and drug-associated morbidity and mortality. They arrived at a number of important findings regarding the reports of methadone-associated mortality and formulated recommendations for reducing that mortality. Their findings and recommendations are summarized in a Report of the National Assessment, which is available on SAMHSA's web site and as a print document; participants' slides and other presentation materials also can be found 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 National Assessment thus can help inform future policy and assure that appropriate access to this important medication is preserved.

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Report of the National Assessment

Presentation Summaries and Speakers' Slides and Handouts

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, which in 2001 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 – for 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. As a result of their deliberations, participants arrived at a number of important findings regarding the reports of methadone-associated mortality and formulated recommendations for reducing that mortality. Their findings and recommendations are summarized in a Report of the National Assessment, which is available on SAMHSA's web site and as a print document; participants' slides and other presentation materials also can be found on the web site.

Part 2. Definitional Issues

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, or quantity of methadone implicated in an individual’s death often are difficult to determine. Thus, the identification and classification of methadone-associated mortality cases may be perceived as encompassing a complex mosaic of many interacting factors that are variously discussed in the literature. Some of these critical factors are depicted as a matrix in *Table 1*.

This matrix is only a tentative overview of possible factors; more a point of departure than a finished product. In general, some of the factors pertain specifically to identifying whether or not methadone itself is a culpable agent in the death, the extent of its involvement if any, and how to classify manner and cause of death. Other factors, such as methadone source and the intention/volition behind its use, might help to determine preventive measures – e.g., educational efforts, closer monitoring of prescribed users – to avert future fatalities.

In developing this document, major electronic databases were searched for resources relating to methadone-associated deaths and the pharmacology/toxicology of methadone. A significant number of epidemiologic databases also were identified and are listed in *Appendix A*. Further case data were gathered from State and Federal sources, as they became available, and were incorporated for informational purposes.

Table 1: Potential Factors in the Identification & Classification of Methadone-Associated Mortality Cases					
Toxicology	Methadone <i>Dose (mg) - Serum Level (ng/mL)</i>		±	Polydrug Involvement <i>Prescribed - Illicit - Alcohol - Other</i>	
Methadone Source	Licit Prescribing/Dispensing <i>OTP Clinic Physician Rx for Analgesia</i>		Illicit Diversion/Unauthorized Use <i>From OTP clinic - Physician Rx - Pharmacy thefts, losses - Other ("street purchase")</i>		
Methadone Formulation	Oral <i>Tablet; Disket; Liquid</i>		Intravenous Injection <i>Manufactured Product; Reconstituted [e.g., crushed tabs]</i>		
Purpose for Methadone Use or Abuse <i>(Intention/Volition)</i>	Therapeutic <i>Maintenance, Opioid Detox, or Pain Rx</i>	Self-Medication <i>Euphoria, Self-Tx Withdrawal, Self-Tx Pain</i>	Suicide <i>Intentional Overdose, Self-Inflicted Harm</i>	Homicide <i>Malicious Intent to Harm Another Person</i>	
Pharmacologic Tolerance Level	Opioid Tolerant <i>Dependence</i>	Methadone Tolerant <i>Dependence</i>	Low Tolerance <i>Occasional Opioid/Methadone Use or Abuse</i>	Opioid Naïve <i>No Tolerance</i>	
Methadone Attribution <i>(Several Classification Schemes in Literature)</i>	Primary – Secondary – Concomitant Suspect <i>Causative – Probable – Possible – Coincidental Agent Methadone-Caused – Methadone-Related – Methadone-Detected</i>				
Morbidity	Pre-existing Medical or Psychiatric Condition <i>(Including Cardiopathology, Long QT Syndrome)</i>		De Novo Pathology Associated with Death <i>(Including Arrhythmia)</i>		
Manner of Death Classification	Natural	Accidental	Suicide	Homicide	Undetermined
ICD-9 Code <i>(International Classification of Diseases [World Health Organization] – no methadone-specific coding)</i>	N965.0 <i>Poisoning by opiates & related narcotics.</i>	E850.0 <i>Accidental poisoning by opiates & related narcotics.</i>	E950.0 <i>Suicide by analgesics, antipyretics, and antirheumatics.</i>	E980.0 <i>Poisoning with undetermined intent by analgesics, antipyretics and antirheumatics.</i>	E935.0 <i>Adverse effect of opiates and related narcotics in therapeutic use.</i>
ICD-10 Code <i>(International Classification of Diseases [WHO] – methadone-specific coding)</i>	X42 and T40.3 <i>Accidental poisoning involving methadone.</i>		X62 and T40.3 <i>Intentional poisoning involving methadone.</i>		Y12 and T40.3 <i>Poisoning with undetermined intent involving methadone.</i> <i>Source ICD 10 Codes: van Laar et al. 2002</i>

Part 3. Recent Concerns About Methadone

Recent press reports of methadone-associated deaths have stirred widespread concern among policymakers and the public. 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.

Other articles and editorials appeared nationwide with the common theme that the upsurge in methadone abuse appeared linked to one of three factors:

- **First**, there have been ongoing increases in abuse of heroin and opioid analgesics and, when other drugs are unavailable, some persons are turning to methadone.
- **Second**, methadone has become more widely available as an increasing number of physicians prescribe it for pain relief.
- **Third**, in at least some States, methadone has become more accessible to unauthorized users as opioid treatment programs (OTPs), following new Federal regulations, have relaxed their policies regarding patients’ take-home doses of the drug (Editorial 2003).

The news articles consistently noted that persons attracted to unauthorized uses of methadone fall into two categories: (1) those addicted to other opioids and (2) naïve users who have not previously used opioids. Most of the articles also acknowledged that methadone often is abused in combination with other drugs and/or alcohol, and that its

abuse is part of an upward trend in *overall* abuse of opioids, which has been recognized as a national problem.

Concerns about fatalities associated with methadone are not new, as extensive surveillance data have documented cases ever since its implementation as an analgesic and, later, in the treatment of opioid addiction. This has been against a background of increasing worldwide drug abuse overall, particularly involving opioid drugs, which are potent agents with capacities for engendering adverse reactions, interactions with other agents, and respiratory depression in overdose, possibly leading to death.

Recent reports from SAMHSA’s National Survey on Drug Use and Health (formerly the National Household Survey on Drug Abuse; 2001, 2002, 2003) show that the number of new non-medical users of prescription drugs has increased steadily since the mid-1980s, especially among younger persons (**Figure 1**). Of particular interest, the number of new non-medical users of opioid pain medications (top line) consistently and sharply increased from 400,000 in the mid-1980s to about 2 million in 2000. These non-medical users are presumed to be abusing drugs primarily for recreational purposes, leading potentially to overdose and/or addiction (ONDCP 1999).

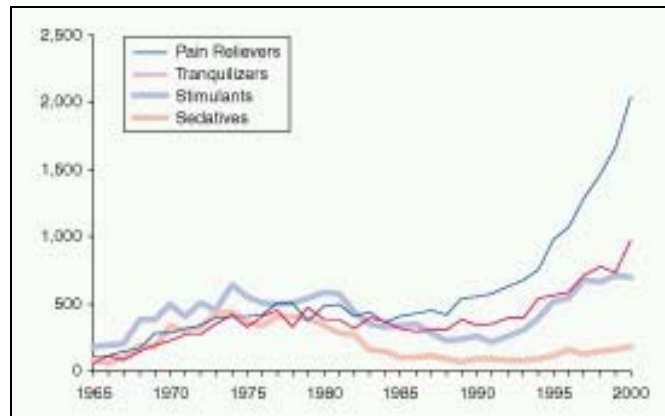


Figure 1: Annual numbers of new non-medical users of prescription-type drugs, by drug category – 1965-2000 (NHSDA, SAMHSA 2001).

SAMHSA’s latest Drug Abuse Warning Network (DAWN) report noted that the incidence of emergency department visits related to opioid analgesic abuse dramatically increased in the U.S. from 1994 and 2001 (SAMHSA 2003; see **Figure 2**). Nationwide, in 2001 alone, opioid analgesics were involved in 14 percent of all drug abuse-related

emergency department visits: there were 21,567 hydrocodone-related and 18,409 oxycodone-related emergency department visits, compared with 10,725 for methadone.

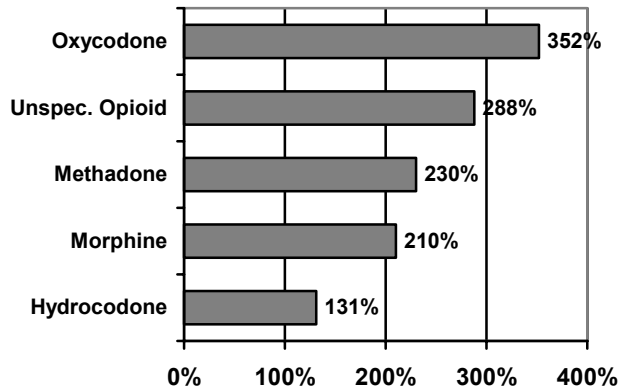


Figure 2: Percentage increase in hospital emergency department visits associated with opioid analgesics, 1994-2001 (SAMHSA 2002).

In 2001, opioid dependence (presumably equating to addiction rather than mere physical dependence) was the most frequently mentioned motive for analgesic abuse, followed by suicide attempts, attraction to psychic effects of the drugs, and unknown or other motives. The average age of persons visiting emergency departments for opioid abuse was 37, numbers of men to women were fairly equivalent, and more than one drug was involved in 72 percent of cases (SAMHSA 2003).

The data suggest that a significant proportion of methadone-associated deaths involve opioids either singly or, more commonly, in combination with other drugs. Male decedents greatly outnumber females and tend to be older than age 30. There also is an apparent proclivity for opioid misusers to abuse more than one drug – such as alcohol, other opioids, sedatives, or tranquilizers – which can enhance CNS-depressant effects of the opioid with potentially fatal outcome. In view of this, it is important to take into account all drugs forensically detected postmortem. This presents a challenge for achieving more accurate forensic determinations of cause of death in these cases, and it highlights the possible need for appropriate case definitions, as well as for improved systems of gathering and classifying premortem or other data for surveillance and prevention purposes (see the discussion at *Part 7*).

Part 4. Pharmacology of Methadone

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).

Methadone's 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 make it an appropriate choice for opioid therapy of pain and addiction (Lobert 2003; Bruera 2002; Payte et al. 1994; Joseph and Woods 1994; Kreek 1992; Ettinger et al. 1979).

Description and Formulations

Methadone is a synthetic opioid analgesic with multiple actions similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. Its principal therapeutic applications are for analgesia and detoxification or maintenance treatment for opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset of action is slower, the course is more prolonged, and the acute symptoms are less severe.

Methadone hydrochloride (3-heptanone, 6-[dimethyl-amino]-4,4-diphenyl-, hydrochloride) is a white, essentially odorless, bitter-tasting powder that is very soluble in water, isopropanol, and chloroform, and practically insoluble in ether or glycerin. Methadone has the empirical formula $C_{21}H_{27}NO \cdot HCl$ and its molecular weight is 345.91 (Mallinckrodt 1995, 2000; Roxane 1995, 1998, 2000). The structural formulas for methadone and its two major metabolites are depicted in **Figure 3**. Methadone undergoes enzymatic *N*-demethylation to form EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), and subsequent *N*-demethylation to EMDP (2-ethyl-5-methyl-3,3-diphenylpyrrolidine) – both of which are inactive metabolites (Moody et al. 1997). Urinary excretion of methadone and EDDP accounts for 17 to 57 percent of a given dose,

depending on urinary pH, and fecal elimination of methadone and metabolites is a secondary route (Eap et al. 2002).

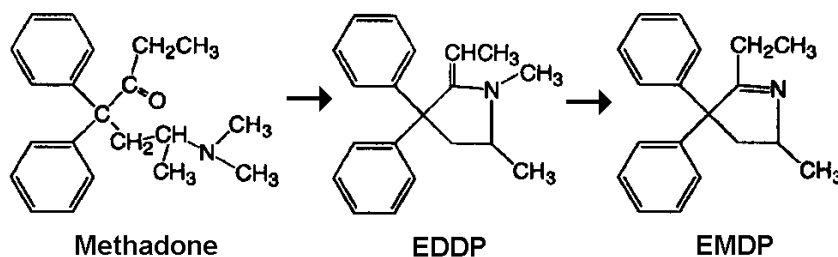


Figure 3: Methadone and its two primary inactive metabolites (adapted from Moody et al. 1997).

Because of its chemical structure, methadone exists in two enantiomeric forms having the same chemical composition but different spatial arrangements, with the enantiomers being mirror images of each other (**Figure 4**). U.S. manufacturers distribute methadone as a 50:50 racemic mixture of the two enantiomers, specified as “R” (also called *levo-* or *l-methadone*) and “S” (*dextro-* or *d-methadone*). Only R-methadone has clinically significant μ -receptor agonist activity, while the S form is essentially inactive as an opioid agonist (Eap et al. 1999, 2002). Early investigations found that the active R enantiomer is metabolized slower and has a lower peak plasma level than S-methadone during stabilized methadone maintenance (Kreek et al. 1979; Nakamura et al. 1982).

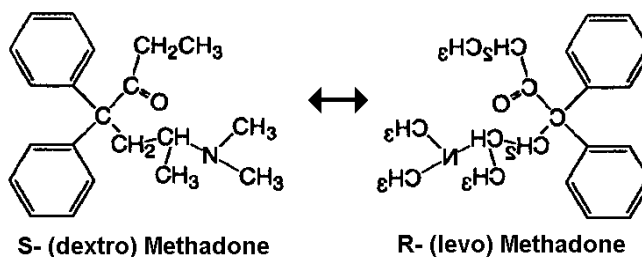


Figure 4: Active ‘R’ and inactive ‘S’ enantiomers of methadone.

Methadone hydrochloride is distributed in several forms: (1) as a powder, primarily for hospital formulary use, (2) as an injectable liquid in multidose vials, and (3) in tablets, diskettes, or premixed liquid concentrate for oral ingestion (Mallinckrodt 1995, 2000; Roxane 1995, 1998, 2000). The three oral formulations are essentially equipotent in effect (Gourevitch et al. 1999) and are the forms most commonly prescribed for outpatient treatment, which also makes them most subject to diversion and/or misuse.

Tablets are supplied in 5 mg (0.0145 mmol) or 10 mg (0.029 mmol) doses, diskets (or diskettes) are 40 mg (0.116 mmol) dispersible tablets, and liquid concentrates contain 10 mg methadone per mL of fluid.

Mechanisms of Action

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 may even reflect external stimuli and environment (Eap et al. 2002, 1988).

Pharmacokinetics

Methadone is up to 80 percent orally bioavailable (compared with 30 percent for morphine). Its elimination half-life averages 24 to 36 hours at steady state, but may

range from as short as 4 hours to as long as 91 hours. Similarly, its rate of clearance from the body can vary by a factor of almost 100. When used in opioid agonist therapy (OAT) – at daily, steady-state oral dosing – methadone should be present in the blood at levels sufficient to maintain an asymptomatic state throughout a 24-hour period, without evidence of opioid overmedication or withdrawal (Inturrisi and Verebely 1972b; Loimer and Schmid 1992; Payte and Zweben 1998). Serum methadone level (SML) and its elimination half-life may be influenced by several factors such as poor absorption, variable metabolism and protein binding, changes in urinary pH, concomitant medications, diet, physical condition, patient age or pregnancy, and even vitamins. Considerable flexibility in dosing is required to stabilize patients in whom methadone pharmacokinetics may be affected by so many factors (Eap et al. 2002; Inturrisi and Verebely 1972a; Leavitt et al. 2000).

Measuring systemic levels of methadone via SMLs – in nanograms per milliliter, ng/mL (see *Appendix C* for conversion factors) – can be a helpful diagnostic aid for achieving adequate dosing in difficult cases. Typically, the methadone serum level peaks about 2 to 4 hours after dosing and gradually declines during the remainder of the 24-hour period to trough level (Inturrisi and Verebely 1972b; Payte and Zweben 1998). Although a strong correlation between methadone dose and trough plasma concentration ($r = 0.82$, $P < .001$) was reported by Wolf et al. (1991), the relationship may not be linear and there also is a need to account for a high degree of interindividual variation among patients and the variable pharmacokinetics of methadone itself (Leavitt et al. 2000).

Other data have also demonstrated a significant relationship between dose and trough SML; however, at each methadone dose there were patients with widely differing serum concentrations, including one SML measurement greater than 1000 ng/mL at a dose of only 120 mg/day (Okruhlica et al. 2002; see *Figure 5*). The rate-of-change ratio between peak and trough SML measures can be a more clinically useful guide, and it has been suggested that the peak SML occurring at 3 to 4 hours post-dosing should be no more than twice the trough level. This would provide an optimal peak-to-trough ratio of 2 or less (Payte and Zweben 1998), which can produce normal peak values exceeding 1000 ng/mL in adequately dosed patients.

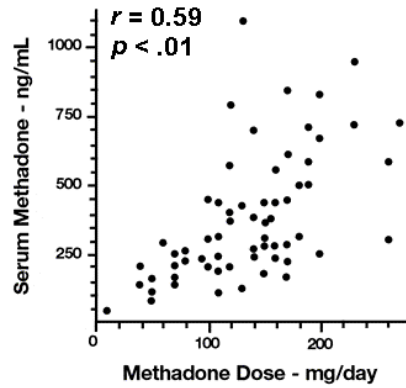


Figure 5: Methadone dose-to-SML relationships in 69 methadone-maintained patients (Okruhlica et al. 2002).

In a recent poster presentation, Dorsey (2003) examined both trough *and* peak SMLs in 37 patients stabilized on methadone maintenance, further demonstrated high variability at each dose interval. All patients were receiving ≥ 110 mg/d of methadone (mean 131 ± 16 mg/d); however, there was a large variance in trough and peak values, along with virtually no correlation between methadone dose and either trough or peak SML ($r = 0.02$ and 0.01 , respectively; see **Figure 6**). For example, one patient at the low end of the dose range (110 mg/d) had a trough = 0 ng/mL (undetectable) and peak = 233 ng/mL; meanwhile, a patient at the highest dose (175 mg/d) had trough and peak values of 0 ng/mL and 180 ng/mL, respectively. The mean peak:trough ratio was 1.6 (95 percent CI: 1.5 - 1.7) and there was a strong linear correlation between peak and trough SML values in these particular subjects ($r = 0.89$, $p < .001$). Thus, it appears that individual methadone *dose* may have poor predictive value for estimating trough *or* peak SML values; although further research seems warranted to clarify this proposition and in which circumstances, if any, the trough SML value might be useful in estimating peak SML.

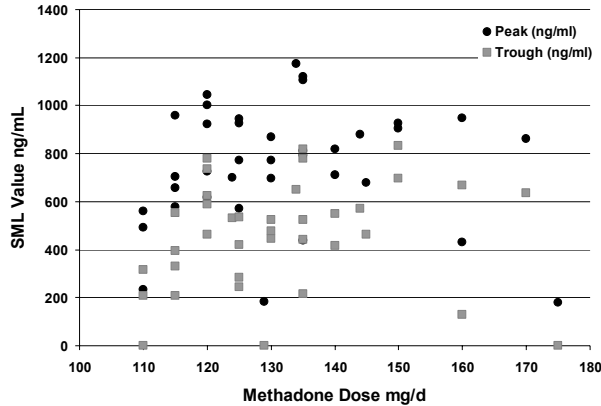


Figure 6: Lack of correlation between methadone dose and either trough or peak SMLs in 37 methadone-maintained patients (Dorsey 2003).

Researchers have affirmed the benefit of a 150 to 600 ng/mL *trough* racemic SML to suppress drug craving and a trough level at or above 400 ng/mL to provide adequate opioid cross-tolerance, making ordinary doses of other opioids ineffective (non-reinforcing or non-euphorogenic) during methadone maintenance (Eap et al. 2002; Leavitt et al. 2000). Today, many practitioners consider a trough SML of 400 ng/mL as adequate therapy for stabilized methadone maintenance; however, clinical studies have demonstrated that methadone doses widely ranging from 50 mg/day to more than 900 mg/day may be necessary to achieve that optimal steady-state trough serum level (Eap et al. 2000). In a cohort of difficult-to-treat patients – with refractory opioid recidivism – all of them achieved opioid abstinence once serum levels of *R-methadone* alone approached 400 ng/mL, which required daily methadone doses greatly exceeding 100 mg in most patients (Eap et al. 2000). Furthermore, clinical research has determined that the formulation of oral methadone – dispensed as either tablet, disket, or premixed liquid – does not differentially affect serum levels (Kreek 1973b; Gourevitch et al. 1999).

Methadone metabolism is largely a function of liver enzyme activity involving cytochrome P450 isoforms (CYP450 enzymes). Drugs that induce activity of these enzymes can accelerate methadone metabolism, abbreviate the duration of its effect, lower the SML, and precipitate abstinence (withdrawal) syndrome. Conversely, CYP450 inhibitors may slow methadone metabolism, raise the SML, and extend the duration of its effects (Kreek et al. 1976; Leavitt et al. 2000; Payte and Zweben 1998). Several CYP450

isoforms – CYP3A4, CYP2D6, and to a smaller extent CYP1A2, and also possibly CYP2C9 and CYP2C19 to a minor degree – are involved in methadone metabolism (Brown and Griffiths 2000; Cozza and Armstrong 2001; Eap et al. 1988, 1999, 2002; Foster et al. 1999). There are genetic and environmental factors acting on these enzymes, leading to a high degree of interindividual variation in methadone pharmacokinetics. Individual differences in the activity of CYP3A4 and CYP1A2, plus a genetic polymorphism of CYP2D6, help account for wide variances in methadone metabolism. As a result, in patients taking exactly the same dose of racemic methadone, corrected for body weight, concentrations of the active R-enantiomer can vary from 1- to 17-fold even in the absence of potentially interacting licit and illicit drugs (Eap et al. 1999, 2002).

(It should be noted that the research and forensics literature assessing methadone concentrations reflects determinations that were made in both blood plasma and serum (which is essentially plasma devoid of fibrinogen and other clotting factors). This results in significant differences in methadone concentrations.)

Pharmacodynamics

Methadone's primary site of action is at μ -opioid receptors; however, R-methadone exhibits much greater affinity at the μ_1 receptor, which mediates supraspinal analgesia, and at the μ_2 receptor mediating spinal analgesia – making R-methadone up to 50 times more potent than the S-methadone enantiomer (Eap et al. 2003). There has been some speculation that the μ_2 receptor is most important in mediating respiratory depression, although this requires further investigation (Sporer 1999; White and Irvine 1999).

Aside from agonist activity at the μ -opioid receptors, both R- and S-methadone exert antagonistic activity at the *N*-methyl-*D*-aspartate (NMDA) receptor (Gorman et al., 1997). This has been observed to counteract opioid tolerance in experimental models of pain (Davis and Inturrisi 1999) and may be the basis for reduced opioid escalation seen in patients treated with methadone, compared with morphine, and may help to explain methadone's superior analgesic effect (Manfredi et al. 2003). The NMDA receptor is a target for glutamate, a primary excitatory neurotransmitter in the brain, although other receptors for glutamate also exist. Blockade of the NMDA receptor can decrease excitability and reduce seizure activity, which makes it of interest in developing therapeutic agents. NMDA receptors also have been implicated to play a role in heroin,

cocaine, alcohol, and nicotine addiction; however, the interaction of methadone and these other agents with respect to the NMDA system has not been elaborated at this time. Of further interest, methadone also inhibits the reuptake of both norepinephrine and serotonin (Codd et al. 1995), and medications sharing this effect have been important in treating depression and in the treatment of neuropathic pain (Manfredi et al. 2003). Methadone's possible adjunctive anxiolytic and/or antidepressant properties, as well as its potential for pharmacodynamic toxicity as a result of drug interactions (e.g., serotonin syndrome) – especially when used in higher therapeutic doses – have not been elaborated.

Pharmacologic Tolerance

Tolerance to opioid effects results in escalation of opioid dose in clinical use for analgesia as well as during abuse for euphoric effects. However, methadone can be toxic to anyone who is not tolerant. A single day's maintenance dose in a tolerant adult can cause life-threatening respiratory depression in an adult who is not tolerant, and as little as 10 mg can be fatal in a child (Harding-Pink 1993). Moreover, opioid tolerance appears to be a complex phenomenon and even experienced users can be at some risk for toxic effects.

According to White and Irvine (1999), it often is erroneously assumed that increasing doses of opioids will *not* have adverse effects on respiratory function because tolerance for the drug's respiratory depressant effects develops at the same rate as tolerance to its euphoric and analgesic effects. However, this is not necessarily the case, and variations in tolerance development across different effects have been demonstrated in animals and humans. Further, some research has shown that tolerance to the respiratory depressant effects of methadone is incomplete; thus, even long-term methadone-maintained patients can be at risk of opioid-induced respiratory depression if there is an acute and large increase in serum level. Moreover, some drugs, such as alcohol and other psychotropic agents, exert their euphoric effects primarily while the blood level of the agent is *rising* (Kramer 2003). Assuming this also is the case with methadone, it would explain why opioid-tolerant users might take extraordinary and/or repeated doses, perhaps in combination with alcohol or other drugs, to achieve a desired state of euphoria and accidentally induce severe respiratory depression in the process.

Opioid tolerance is influenced by changes at receptor sites (pharmacodynamic tolerance) and in opioid metabolism or distribution (pharmacokinetic tolerance), as seen in chronic dosing. It also has been shown that the degree of tolerance can be influenced by environmental factors, whereby certain cues previously associated with the drug can markedly enhance tolerance, compared with less tolerance observed when drug is administered in a novel environment. In short, administration of opioid in an environment not previously associated with the drug can foster reduced tolerance and higher risk of overdose (White and Irvine 1999).

As a possible explanation for differential tolerance, White and Irvine (1999) suggest that the euphoric and respiratory depressant effects of opioids are mediated by different brain regions. The function of the limbic and cortical regions, mediating euphoria, may adapt more quickly and readily to drug effects and are more susceptible to environmental conditioning factors; whereas, brainstem regions controlling respiration may be less adaptable. Furthermore, reduced tolerance over time – such as, during a period of diminished opioid use or abstinence – can result in much greater effect per given dose of opioid if/when opioid use is resumed. That is, a dose that previously had euphoric effects with minimal respiratory depression may suddenly produce severe respiratory impairment. White and Irvine say this indicates that many persons who die of opioid overdose may have had a period of lower than normal opioid use and hence a loss of tolerance prior to overdose; however, definitive information on the relative rate of tolerance loss to the analgesic, euphoric, and/or respiratory effects of opioids is lacking.

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).

Dosing, Overdose and Toxicity

Some patients have reported a degree of “somatic distress” even after 12 months of continuing methadone maintenance. These complaints – including sweating, constipation, drowsiness, sexual problems, and aches in bones and joints – have not hindered patient retention in treatment (Bell and Zador 2000). Although studies have not correlated methadone dose or blood levels with the distressing signs and symptoms, they could denote either methadone under- or over-medication in some cases.

A parenteral dose of 8 to 10 mg of methadone is approximately equivalent in analgesic effect to 10 mg of morphine, and with single-dose administration the onset and duration of analgesic action of the two drugs are similar. The combination of methadone’s opioid agonistic activity, antagonism at the NMDA receptor, and the inhibition of catecholamine reuptake, either additive or synergistic, may explain why a substantial number of patients with pain refractory to other measures achieve selective and effective analgesia with methadone and methadone only (Manfredi et al. 2003).

When administered orally, methadone is approximately one half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak serum level, and an increase in the duration of analgesic effect. Methadone *analgesia* effects peak between 1 and 2 hours and last 3 to 5 hours (Ettinger et al. 1979). The manufacturer-recommended adult dosage for analgesia is 2.5 mg to 10 mg every 3 or 4 hours as necessary, although some have suggested that the higher dose is excessive and potentially lethal until tolerance is well-established over several days (Ettinger et al. 1979). Dosage is adjusted according to the severity of the pain and the response of the patient. Occasionally, it may be necessary to exceed the usual dosage recommended in cases of exceptionally severe pain or in those patients who have become tolerant to the analgesic effect of opioids (Mallinckrodt 1995; Roxane 2000).

Dosing regimens for opioid detoxification or maintenance treatment are quite different than in pain management. To begin, it is suggested that an initial single dose of 15 to 20 mg of methadone will often be sufficient to suppress opioid withdrawal symptoms, although higher doses may be needed for patients physically dependent on high doses of opioids (Mallinckrodt 1995, 2001). Federal regulations specify “the initial dose of methadone shall not exceed 30 milligrams and the total dose for the first day shall not exceed 40 milligrams, unless the program physician documents in the patient’s record that 40 milligrams did not suppress opiate abstinence” (Federal Register 2001).

Numerous reports have commented on the increased risk of death in the early stages of methadone maintenance – the *induction period* (Bell and Zador 2000; Caplehorn and Drummer 1999; Clark et al. 1995; Drummer et al. 1990, 1992; Gardner 1970; Harding-Pink 1991). Death in these cases usually occurs at home during sleep, many hours after peak pharmacokinetic blood concentration has occurred, which is in contrast to the more rapid death typically following IV-methadone overdose (Segal and Catherman 1974).

The increased death rate during induction is recognized as largely due to difficulties in assessing the opioid dependence status of new patients. For example, some individuals who claim to be regular users of heroin or other opioid drugs may be either occasional users or opioid-naïve. Occasional opioid use does not engender physical tolerance; thus, if such individuals are started on a program at doses in excess of their established tolerance, it can lead to fatal consequences (Baden 1978; Gardner 1970). Moreover, new opioid users take longer to clear methadone from their systems, placing them at greater risk of overdose (Karch and Stephens 2000). Oral methadone doses as low as 20 mg can be fatal, particularly after several days of treatment, because of accumulation of drug in blood and tissues (CDHAG 2000).

The risk of death in persons beginning methadone maintenance (in countries without a 40 mg initial day dose cap) has been calculated as 7-fold higher than their risk prior to entering the OAT program (Caplehorn and Drummer 1999). This risk is nearly 98 times greater for new patients than for patients who have safely received methadone for more than two weeks (Karch and Stephens 2000). Some researchers have noted that a consistent finding in deaths that occur during the induction period is the involvement of multiple drugs (Bell and Zador 2000). Risk declines substantially after stabilization on methadone and reductions in illicit drug use during ongoing participation in an OTP.

A long-standing difficulty has been the diversion or theft of legally prescribed methadone by unauthorized persons (Cairns et al. 1996; Williamson et al. 1997), and this is a factor in many fatalities (Zador and Sunjic 2000). Because of its long half-life and consequent potential for accumulation, inappropriately used methadone may be more dangerous than heroin (CDHAG 2000). Recently, concerns have centered on the diversion or theft of methadone tablets prescribed for pain and their use for recreational purposes, often by opioid-naïve users.

The primary toxic effect of excessive methadone is respiratory depression with pulmonary edema and/or aspiration pneumonia (Harding-Pink 1993). White and Irvine (1999) have postulated that the effects of exogenous opioids, such as methadone, on respiration include changes in both tidal volume (the amount inhaled and exhaled with each breath) and respiratory frequency. Low concentrations of opioids appear to mainly depress tidal volume, whereas at higher concentrations both tidal volume and respiratory frequency are affected.

Lethal Interactions With Other Agents

Long ago, Roizin and colleagues (1972) called attention to the “poison cocktail” that may result from the ingestion of multiple drugs, including methadone. It has been recommended that explorations of potentially lethal drug-drug interactions should include examinations of altered absorption, distribution, tissue uptake, metabolism, and excretion, as well as the consideration of possible “toxicodynamic” (toxic pharmacodynamic) interactions at receptor sites (Borron et al. 2001).

Haberman and colleagues (1995) suggest that pharmacologic interactions between psychotropic drugs can be *additive*, so that the net effect is the sum of the substances’ individual effects, or *supra-additive* (synergistic or potentiating) when the combined effects are greater than additive. For example, it has long been observed that tranquilizers and hypnotics taken together may potentiate the depressant effects of each drug and of alcohol, so that the combination can produce fatal toxicity even at doses that would appear moderate when considered separately (Roizin et al. 1972). Similarly, alcohol and benzodiazepines often have been implicated with opioids in drug overdoses. In themselves, alcohol and benzodiazepines are relatively moderate respiratory depressants, but when combined with a potent opioid they can augment the opioid’s effects (White and Irvine 1999). In an animal model, Borron et al. (2001) found that the benzodiazepine flunitrazepam – which is not approved in the U.S., but is physiologically similar to and 10 times more potent than diazepam – doubled the lethality of methadone but not that of morphine in treated rats. The authors suggest that alterations of methadone metabolism by the benzodiazepine, or vice versa, was an insufficient explanation for this outcome, and that modified effects at binding sites for each drug may play an important role.

Similarly, alcohol acts as an antagonist at the NMDA receptor and thus enhances GABA effects by increasing duration of Cl⁻ channel opening (White and Irvine 1999); accordingly, respiratory depression may be at least theoretically potentiated by a pharmacodynamic interaction due to methadone's additive (or, perhaps, synergistic) antagonism of the NMDA receptor.

Cardiac Effects

There has been recent interest in methadone's possible role in QTc prolongation potentially leading to torsade de pointes (TdP). Laboratory experiments have demonstrated effects of high-concentration methadone on electrical conduction in various cell and tissue types (Horrigan 1990; Huidobro 1971; Lee and Berkowitz 1977; Mantelli et al. 1986; Rendig et al. 1980; Seyler et al. 1983; Wu et al. 1994, 1997a, 1997b). The most recently reported laboratory evidence suggests that methadone, but not its metabolite EDDP, blocks cardiac HERG K⁺ currents (Katchman et al. 2002), which have been associated with arrhythmogenic properties in the clinical setting (Tomargo, 2000). In the study by Katchman and colleagues, fentanyl and buprenorphine also blocked cardiac HERG K⁺ currents; however, the authors noted that this does not necessarily mean that these agents or methadone cause arrhythmias, since other factors, such as the degree of protein-binding in plasma, could have significant influence on the ability of these opioids to block HERG currents in vivo. The researchers also commented that 89 percent of plasma methadone is protein-bound, thereby possibly reducing the in vivo amount of methadone available to inhibit I_{HERG} to 11 percent (free fraction) and raising the therapeutic index for methadone approximately 10-fold.

Existing evidence in humans of noteworthy QTc prolongations associated with oral methadone, and their potential for inducing TdP, has been primarily limited to case reports (Bittar et al. 2002; Krantz et al. 2002), and factors other than methadone may have played a role in causing arrhythmias in many of these patients. In the largest case series (Krantz et al. 2002), 9 of 17 patients developing TdP were receiving methadone maintenance treatment and 8 were receiving oral methadone for pain. Approximately 82 percent (14/17) of patients had known risk factors for arrhythmias, such as hypokalemia, or were concomitantly taking other drugs that could prolong the QT interval. Therefore,

the authors have cautioned that “Our report should not be interpreted to suggest that high-dose methadone cannot be used safely.”

Prospective clinical investigations in the past have indicated minimal or no cardiotoxic effects solely attributable to oral methadone used during OAT at stable doses (Huber et al. 2001; Mathot et al. 2002; Stimmel et al. 1973). A recent poster presentation by Martell and associates (2003) reported on cardiac status in 151 methadone maintained patients at 2 months after enrollment (i.e., following induction) and in 135 patients at a 6-month followup assessment. Statistically significant mean increases in QTc interval compared with baseline were observed at 2 months (10.6 msec increase; mean 429 ± 22 msec) and 6 months (12.1 msec increase; mean 430 ± 23 msec). The authors concluded that these QTc prolongations were modest and of uncertain clinical significance, since there was no increase greater than 40 msec, or QTc > 500 msec, or any TdP incidents. There was limited power in this study to accurately gauge effects of illicit drugs taken during treatment on cardiac conduction, plus 47 percent of ECGs were abnormal at baseline, with sinus bradycardia being most common. Also, the authors did not report on possible methadone dose or SML effects on the QTc interval, although doses ranged only up to 150 mg/d in these patients.

There is still the question of whether oral methadone doses significantly higher than those typically used in many OTPs might engender cardiac risks. A case series from one large program profiling 12 patients receiving ≥ 500 mg/d of methadone (mean 812 ± 249 mg/d; range 500 - 1400 mg/d) found that females exhibited higher mean QTc values than males (460 vs 422 msec), as would be expected; however, the overall mean QTc interval – 435 ± 45 msec – was within acceptable limits (Leavitt 2001). All patients were taking comedications and many had physical illness, such as HIV, hepatitis, liver cirrhosis, hypertension, and diabetes; although, none of the patients exhibited signs or symptoms of cardiac distress. There was a moderate, but nonsignificant, correlation between methadone dose and QTc interval ($r = 0.53$; $p = 0.08$). In a larger study by Huber et al. (2001), the dose/QTc correlation was weak and nonsignificant ($r = 0.20$; $p = 0.08$), and there were only very weak, nonsignificant associations between QTc changes and methadone peak or trough plasma levels, with correlation coefficients ranging from 0.01 to 0.18 (p range = 0.92 - 0.26).

Potential cardiotoxic effects of methadone in naïve users (i.e., those without established tolerance) are largely unknown. Cardiac conduction disturbances putatively associated with methadone abuse by such persons and leading to death would not be detected at autopsy; however, preexisting cardiovascular disorders, which are relatively prevalent in the U.S. population, are sometimes discovered and reported. According to current estimates, nearly 61 million Americans have cardiovascular disease, including coronary artery disease (CAD), which is the leading cause of death in the Western world. There are an estimated 300,000 to 400,000 sudden cardiac deaths each year in the U.S., most of which are due to ventricular arrhythmias. Further, long QT syndrome (LQTS) potentially influencing dysrhythmias may be more common than presently imagined: an investigation at one institution found the prevalence of LQTS of unknown origin was 7 percent among more than 34,000 patients undergoing routine ECGs during a six-month period (Kocheril 1997).

Persons who abuse multiple drugs, those on methadone maintenance, and naïve users of methadone all are part of this larger demographic, although the risks of each group may be magnified by former and/or current abuse of illicit drugs or alcohol, particularly cocaine because of its known cardiotoxic effects (Symanski and Gettes 1993). Further, a significant proportion of opioid-addicted persons have drug-induced cardiac abnormalities, including cardiomegaly, infectious endocarditis, coronary artery abnormalities, acquired valvular disease, primary or secondary myocardial heart disease, pulmonary-associated heart disease, and congenital cardiac anomalies.

Illicit drug users and alcoholics also are exposed to a number of general health risks and infectious diseases and are less likely to receive regular health care. Also, some persons with suspected drug-induced LQTS may, in fact, have an underlying genetic predisposition. The percentage of patients harboring silent, asymptomatic genetic abnormalities of ion channel structures, and potentially prone to developing TdP with drugs well-tolerated by most persons, may be larger than is commonly assumed (Backmund et al. 2001a; Glauser et al. 1977; Hampton 2003; Hser et al. 2001; Mathot et al. 2002; Stimmel et al. 1973; Takehana and Izumi 2000).

Part 5. Methadone in Opioid Agonist Therapy

Methadone was approved in the United States by the Food and Drug Administration in 1947 as an analgesic and, by 1950, it was being used to treat the painful symptoms of withdrawal from opioids, usually heroin (Payte 1991; Rettig and Yarmolonsky 1995). In 1964, it was discovered that a continuous, daily maintenance dose of oral methadone offered a number of beneficial effects, allowing otherwise debilitated opioid-addicted persons to function more normally (**Table 2**: Bell and Zador 2000; Dole 1988; Joseph and Appel 1993; Joseph and Woods 1994; Joseph et al. 2000; Kreek 1992, 1993; Payte and Khuri 1993a; NIH 1997; Stine et al. 1998 Zweben and Payte 1990).

Table 2: Benefits of Daily Oral Methadone Maintenance

- A stable maintenance dose of methadone does not make the patient feel either “high” or somnolent, so the person can socialize, work or go to school, and generally carry on a normal life.
- Methadone can be taken orally once daily or in split doses, helping to limit exposure to injection-borne diseases like hepatitis and HIV.
- Methadone’s gradual, long-lasting effects eliminate drug hunger or craving, unlike the rapid ups and downs of short-acting opioids which lead to strong desires for more drug.
- Daily drug-seeking to “feed a habit” becomes unnecessary, and the euphoria-blocking effect of cross tolerance makes other opioids undesirable.
- Once a stable dose is reached, there is little change in tolerance to the therapeutic effects of methadone, so it does not take increasingly more of the medication to achieve the same results.
- Methadone has a favorable safety profile, with minimal side effects.

Since the mid-1960s, methadone maintenance has been studied more thoroughly as a modality for the treatment of opioid addiction than any pharmacotherapy for any addiction, and with uniformly positive results (Joseph et al. 2000; Newman 2001; NIH 1997; ONDCP 1999; Rettig and Yarmolonsky 1995). Opioid agonist therapy (OAT) generally is used to describe the use of methadone to treat addiction in an opioid treatment program (OTP).

Beginning with only 400 patients in 1968, the number of persons being treated with methadone in OTPs in U.S. has grown steadily over the years to more than 200,000 patients in nearly 1,200 registered programs in 45 States (excluding only Montana, Idaho, North Dakota, South Dakota, and Mississippi, all of which still prohibit OAT), as well as the District of Columbia, Puerto Rico, and the Virgin Islands (SAMHSA, 2003 data). However, the number of programs and their patient capacities have not grown sufficiently to serve the growing numbers of patients who need treatment. For each patient who receives OAT, up to four or more persons need treatment but find it unavailable (Federal Register 1999, 2001; ONDCP 1999, 2000; Payte and Zweben 1998).

As with any dose-dependent medication, an adequate methadone dose has been found to be critical to therapeutic success, and continued opioid use or relapse to addiction can be virtually eliminated by proper methadone-dosing practices. Initial research has shown that 80 to 120 milligrams of methadone per day, on average, is optimal for many patients (Dole 1988). Such adequate doses result in better treatment outcomes, as measured by increased retention of patients in treatment and less illicit drug use.

For several reasons, including physical condition, mental status, interactions with other medications, or prior use of high purity street heroin, some patients require significantly greater daily methadone doses for treatment success – doses often exceeding 200 mg/day or more (Gordon 1994; Payte and Khuri 1993a; Stine et al 1998).

At one time, some authorities expected that methadone could be used simply as an agent to transition patients to drug-free lifestyles, including eventual withdrawal from methadone itself (NIH 1997; Payte and Zweben 1998). However, only 54 to 73 percent of patients are able to successfully complete medically supervised methadone withdrawal programs, and nearly three-quarters of such patients relapse to drug abuse within just six months (Backmund et al. 2001). Research has further demonstrated that virtually all patients who complete a supervised methadone withdrawal program or otherwise discontinue methadone, and do not pursue additional and continuing therapy, eventually relapse to opioid abuse, with correspondingly high mortality rates (Bell and Zador 2000; Joseph et al 2000; Magura and Rosenblum 2001; Rosenblum et al. 1991; Zanis and Woody 1998).

Based on a review of the research, Bell and Zador (2000) concluded that methadone maintenance therapy does not necessarily enhance the potential for eventual abstinence from opioids; however, there are significant quality of life and health benefits to be gained during methadone maintenance that overshadow any negative connotations of continued dependence on opioid medication. For example, mortality from all causes in methadone-treated patients is typically many-fold lower than in untreated opioid addicts (NIH 1997), and studies have consistently shown that the risk of communicable infection is significantly reduced by participation in opioid treatment, even in patients who cannot achieve total abstinence from illicit drugs (Leshner 1999; Federal Register 1999, 2001).

An early and large study in New York City that followed 17,500 methadone maintenance patients from 1965 to 1971 found that the mortality rate from all causes for persons receiving OAT with methadone was similar to that for the general population. By contrast, mortality in untreated heroin addicts was more than 15 times higher (Gearing and Schweitzer 1974). Roizin and colleagues (1972) have reported that the fatality rate among methadone-maintained patients is between 1 and 1.3 percent, but increases to 10 percent among those who are discharged from or who voluntarily discontinue treatment.

Recent epidemiologic studies have supported these early results, confirming the protective effects of methadone maintenance and demonstrating that the relative risk of death is three to four times *lower* for an individual continuing in an OTP compared with one who discontinues treatment (Bell and Zador 2000; CDHAG 2000).

Deaths occurring during induction into methadone maintenance have been reduced as physicians have become better educated in prescribing methadone. An important factor has been the limits placed on the initial dose (30 mg.) and the first day's dose (40 mg.) by the FDA, and continued by SAMHSA when it assumed responsibility for regulation of OTPs in 2001.

Part 6. Methadone Abuse and Associated Mortality

Methadone was widely used in clinical medicine as an analgesic and antitussive long before maintenance therapy for opioid addiction was introduced in the 1960s. According to a brief review by Harding-Pink (1993), early indications for methadone included migraine, dysmenorrhea, labor pain, trigeminal neuralgia, advanced cancer or tuberculosis, tetanus, and temporary treatment of opioid withdrawal symptoms. Almost from its earliest use, however, deaths have been associated with methadone.

During an early clinical trial in the late 1940s, methadone was implicated in the death of one patient and associated with severe respiratory depression in another. In the 1950s, several deaths were reported in England and Germany among young children exposed to methadone, typically in cough syrups, and other fatalities were reported in countries where methadone was widely used. Because of its perceived toxicity and dependence liability, methadone largely fell into disuse by the early 1960s (Harding-Pink 1993), although there has been renewed and growing use of methadone as an analgesic in recent years.

With its introduction as maintenance therapy for opioid addiction during the mid-1960s, methadone regained its place in medical practice. Worldwide consumption of methadone rose rapidly and exponentially. However, there also were cases of poisoning associated with methadone in many cities that instituted OAT programs (Harding-Pink 1993; also see *Appendix B*).

There also have been sporadic reports of inadvertent poisonings among the children or family members of methadone-treated patients, especially when methadone was distributed for take-home use in liquid forms and packaging that masked its identity to the uninformed (Harding-Pink 1993).

National Data on Abuse of Methadone and Related Drugs

Recent reports from SAMHSA's National Survey on Drug Use and Health (formerly the National Household Survey on Drug Abuse; 2001, 2002, 2003) show that the number of new non-medical users of prescription drugs has increased steadily since the mid-1980s, especially among younger persons (*Figure 7*). Of particular interest, the number of new

non-medical users of opioid pain medications increased from 400,000 in the mid-1980s to about 2 million in 2000. These non-medical users are presumed to be abusing drugs primarily for recreational purposes, leading potentially to overdose and/or addiction (ONDCP 1999).

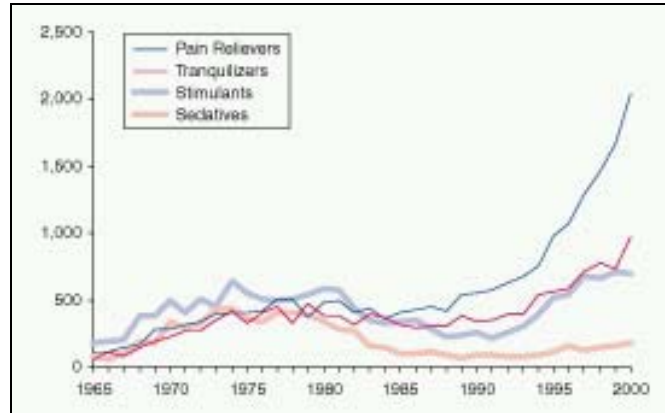


Figure 7: Annual numbers of new non-medical users of prescription-type drugs, by drug category – 1965-2000 (NHSDA, SAMHSA 2001).

In 2001, opioid dependence was the most frequently mentioned motive for analgesic abuse, followed by suicide attempts, attraction to psychic effects of the drugs, and unknown or other motives. The average age of persons visiting emergency departments for opioid abuse was 37, numbers of men to women were fairly equivalent, and more than one drug was involved in 72 percent of cases (SAMHSA 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).

From 1994 to 2001, SAMHSA’s Drug Abuse Warning Network (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).

Moreover, SAMHSA’s latest Drug Abuse Warning Network (DAWN) report show that the incidence of emergency department visits related to opioid analgesic abuse dramatically increased in the U.S. from 1994 and 2001 (SAMHSA 2003; see *Figure 8*). Nationwide, in 2001 alone, opioid analgesics were involved in 14 percent of all drug abuse-related emergency department visits: there were 21,567 hydrocodone-related and 18,409 oxycodone-related emergency department visits, compared with 10,725 for methadone.

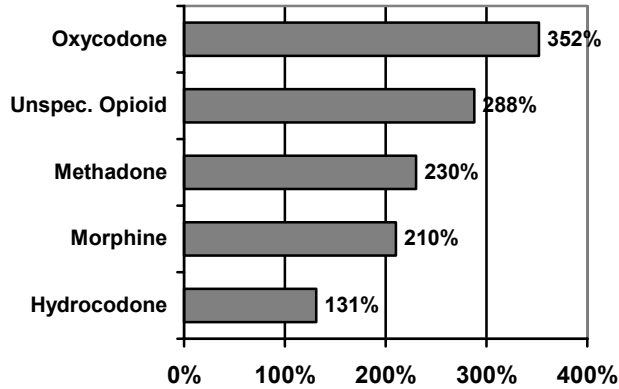


Figure 8: Percentage increase in hospital emergency department visits associated with opioid analgesics, 1994-2001 (SAMHSA 2002).

National Data on Methadone-Associated Mortality

Federal data show that a significant proportion of methadone-related deaths involve opioids either used alone or, more commonly, in combination with other drugs. Males greatly outnumber females among decedents, most of whom are older than age 30.

Data from MedWatch – the FDA’s Safety Information and Adverse Event Reporting Program – indicate that, from 1970 through 2002, 1,114 cases of methadone-associated deaths in adults were reported. Critically, a greater number of methadone-associated deaths were reported in 2001 alone than during the entire period from 1990 through 1999; this number doubled again in 2002 (*Figure 9*). These excluded duplicate reports, deaths in children (including fetuses [stillborn] and infants), and cases from outside the U.S.

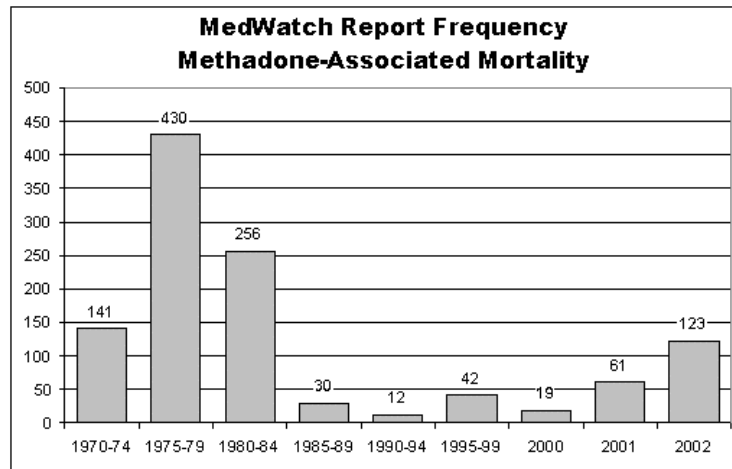


Figure 9: Trends in FDA MedWatch data reporting methadone-associated deaths.

It should be noted that the FDA’s AERS system relies on voluntary participation by providers (although reporting is mandatory for events known to a pharmaceutical company that markets the drug in question) and only a small proportion of all actual cases are submitted, resulting in underreporting, typical for a passive surveillance system. For example, during the early 1970s, Barton (1975) obtained information on methadone-associated deaths by contacting medical examiners and coroners across the U.S. He found that, for 25 areas of the country providing usable data, there were 156 deaths involving methadone in 1971 and 332 such deaths in 1972 – a 113 percent increase, possibly due to rapid growth in under-regulated methadone programs during that time. In the FDA data noted above, there were only two cases in 1971 and six cases in 1972 reported via the MedWatch system. Still, AERS data represent a large and long-running passive surveillance system that yields a number of case reports; it is possible that observed trends may be more important than actual numbers of reports for each year.

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 rather than, or in addition to, methadone (Litovitz et al. 2002; Fingerhut and Cox 1998; Cone et al. 2003; Eastwood 1998). This continues a trend that has been developing over a number of years. As shown in **Figure 10**, virtually all increases in poisoning deaths between 1985 and 1995 involved drugs, with the death rate in males for that category nearly tripling (from 5.5/100,000 population to 16.1/100,000) and the rate

for females increasing 60 percent (to 6.0/100,000). In particular, the male death rate associated specifically with opioids (ICD-9 codes E850 and 305.5) increased more than three-fold, from 1.1 to 3.5 per 100,000, and comparable rates for females also increased but less dramatically so (Fingerhut and Cox, 1998).

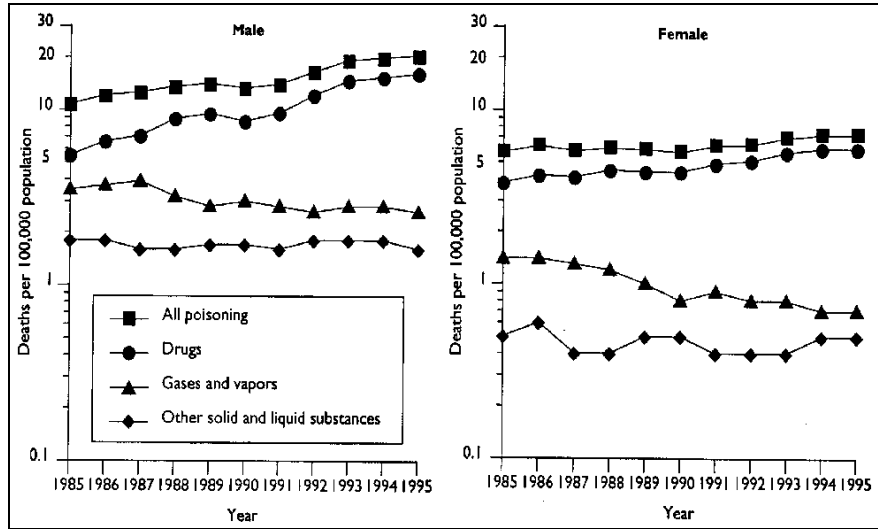


Figure 10: Poisoning death rates for males and females ages 35-54 during 1985-1995 (Fingerhut and Cox, 1998).

Poison control center data for 2001 (Litovitz et al. 2002) show that 1.7 percent of all reported poison exposure cases in the U.S. (approximately 39,000) were related to intentional drug abuse; that is, resulting from the intentional improper use of a substance where the victim likely was attempting to achieve a euphoric or psychotropic effect. Of 1,074 fatalities reported by poison control centers, 144 resulted from intentional substance abuse, most commonly involving opioid analgesics, followed by sedative/hypnotics, antidepressants, and “street” drugs/stimulants. However, such poison control center reports are known to underreport drug-related fatalities. Considering all causes (i.e., intentional and otherwise), oxycodone products were implicated in 54 deaths and hydrocodone products in 47. Most notably, there was a sharp increase in long-acting oxycodone product deaths, from 8 in 2000 to 21 in 2001, with roughly half (11/21) involving polysubstance abuse. Nearly 2,000 methadone exposures were reported to poison control centers in 2001 (including 1,109 intentional abuse cases) resulting in 36

deaths overall; however, multiple substances were involved in 15 of 23 (65 percent) of fatal methadone cases that were summarized in detail.

Three primary scenarios are seen in methadone-associated deaths:

1. Accumulations to toxic levels during the start of opioid detoxification or beginning methadone maintenance treatment (i.e., the induction period prior to methadone steady-state and tolerance development) or in pain management with legitimately dispensed methadone;
2. Misuse of diverted methadone by essentially opioid naïve persons or by those who have diminished opioid tolerance; who also may take excessive and/or repetitive doses in an attempt to achieve euphoric effects;
3. Additive or synergistic effects of other CNS-depressant agents – e.g., benzodiazepines, alcohol, heroin or other opioids – taken in conjunction with methadone (primarily taken for abuse) by either opioid-naïve or opioid-tolerant individuals, although the amounts fostering toxicity and death would vary across individuals.

Research suggests that methadone dose amounts and blood concentrations do not necessarily predict outcome. Further, isolated postmortem serum concentrations of methadone do not appear to reliably discriminate between victims who have died from methadone toxicity and cases in which the presence of methadone is purely coincidental. This presents a challenge for achieving more accurate forensic determinations of cause of death in these cases, and it highlights the possible need for appropriate case definitions, as well as for improved systems of gathering and classifying premortem or other data for surveillance and prevention purposes.

Currently available data do not implicate OTPs as a significant source of methadone in fatality cases. In the instances in which the exact source was known and reported, methadone originated from OTPs infrequently; whereas solid forms (tablets), primarily prescribed for pain and distributed through pharmacies or hospitals, appeared to be a more common source of methadone associated with deaths. Methadone dispensed by OTPs is almost entirely in the liquid form, although the new regulations (42 CFR 8) did, for the first time in 2001, allow for the use of solid methadone in OTPs. Liquid methadone is rarely used for outpatient pain control.

Moreover, while reports of methadone-associated fatalities have increased during recent years, epidemiologic data strongly suggest that these incidents were on the rise *prior to* the institution, in 2001, of revised Federal regulations governing OAT programs that liberalized methadone dispensing and take-home allowances for stabilized patients (Federal Register 2001, 42 CFR Part 8).

Additionally, the new provisions in the regulations have been adopted at a very slow pace. For example, in Florida, less than one percent of all patients in methadone treatment are receiving take-home methadone at intervals greater than once every 14 days (Phil Emenheiser, Florida State Methadone Authority, personal communication, March 2003). At the same time, there has been a renewed awareness in the medical community of methadone's value as an analgesic, with a corresponding increase in its use and potential for diversion, misuse, or even iatrogenic overdose. This has coincided with increases in the prescribing of *all* opioid-analgesics as physicians have become more sensitive to providing adequate and effective pain management for patients who need it. Therefore, methadone's expanded distribution, availability, and consequent reports of misuse (and associated deaths) must be considered within the context of increased availability of methadone for analgesic purposes, as well as growing abuse of *all* opioid medications.

State Data on Methadone Abuse and Associated Mortality

At the state level, concerns have been sparked by local 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). The data suggest a correlation between increased pharmacy distribution of methadone tablets for pain management and increased problems with methadone, including methadone-associated deaths.

Maine. In Maine, surveillance data depict an increase in methadone-associated fatalities that roughly paralleled the increase in all drug deaths between 1997 and 2002 (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).

The rate of overall accidental drug-overdose deaths in Maine, as well as the rate attributable to methadone, rose significantly during 2000 and 2001, and both were expected to increase again during 2002 (*Figure 11*). Methadone-caused and methadone-related deaths, together, constituted nearly one-third (31 percent) of Maine's 248 accidental poisoning deaths during 1997-2002 (projected) in a State with a population of only 1.2 million (Sorg 2002).

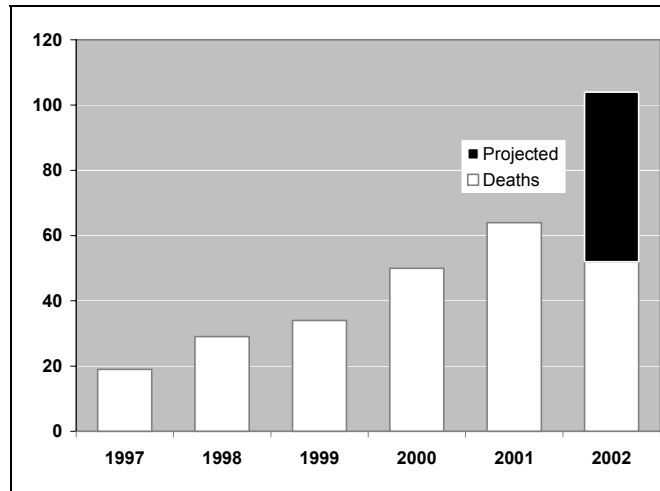


Figure 11: Accidental overdose deaths in Maine, 1997-June 2002 (Sorg 2002).

Drug-related deaths increased statewide, but were concentrated in Cumberland County, which includes Portland and is one of the most populous of the 16 counties in the State. From January through June 2002, there were 10 methadone-caused and 4 methadone-related deaths in Cumberland County, as defined by medical examiners, with another 26 total cases projected for the remainder of 2002. About half of the deaths were in Portland. However, only a small proportion of decedents were receiving methadone from OAT clinics or by prescription from pharmacies for pain (Sorg 2002). In a preliminary analysis of 23 methadone-related deaths from Cumberland County in 2001 and 2002, only 3 (13 percent) decedents were in OTPs, while 2 others (9 percent) had methadone prescriptions for pain (Sorg and Greenwald 2002), and the remaining 18 obtained methadone via unspecified sources.

From 1997 through June 2002, the trend in methadone-associated overdoses roughly paralleled cases of non-methadone-associated drug deaths, except for an upsurge in 2000 (*Figure 12*). During the entire period, there were 77 confirmed methadone-associated deaths in which methadone toxicity was either classified as a primary or underlying cause (N=52, 68 percent) or listed as a significant factor or as one agent in an undifferentiated mixed-drug-caused case (N=25) (Sorg 2002). Deaths with methadone identified in their toxicology doubled between 1999 and 2000, with a leveling in 2001, and the total for 2002 was projected to be more than double that of 2001 (Sorg and Greenwald 2002).

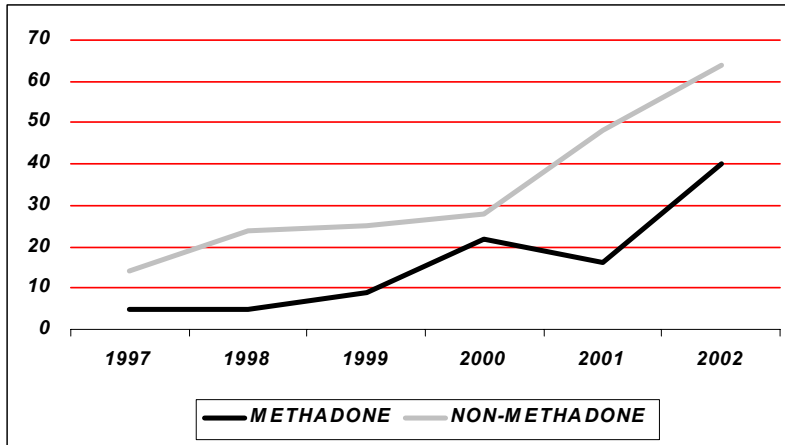


Figure 12: Accidental overdose trends comparing methadone (bottom line) and non-methadone (top line) deaths during 1997-2002 in Maine (Sorg 2002).

Opioid analgesics were prevalent in a majority of drug-associated deaths in Maine, with one or more opioids present in 71 percent of decedents and identified as a cause of death in 53 percent of those cases. Overall, the top two opioid drugs were methadone and heroin/morphine, followed by oxycodone (**Figure 13**). The most frequently occurring opioid drug combinations were heroin-codeine, methadone-oxycodone, and heroin-methadone. However, alcohol also was commonly associated with opioid and non-opioid deaths (Sorg and Greenwald 2002).

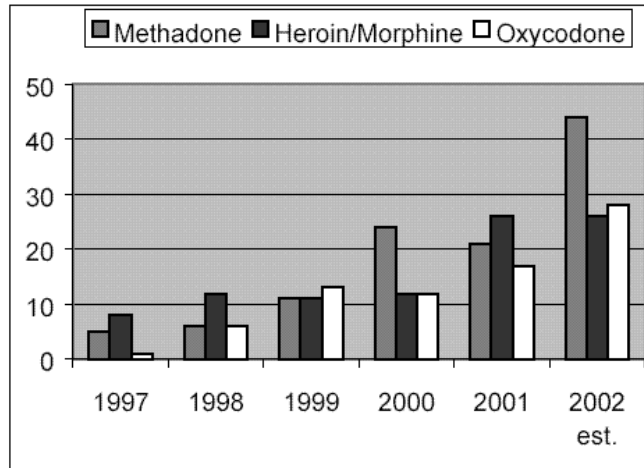


Figure 13: Number of cases in which key drugs were identified in Maine cases, based on toxicology, 1997-2002 (Sorg and Greenwald 2002).

A detailed examination of 23 methadone-associated death case descriptions from Cumberland County reveals a number of important comorbid factors that might have contributed to the risk of overdose fatality (see **Figure 14**; Sorg 2002). There appeared to

be significant proportions of underlying conditions, both physical and mental, along with concomitant medication/drug use among the decedents. Sorg and Greenwald (2002) commented that, overall, there was a high prevalence of mental illness and physical conditions (such as, heart, lung, and liver disease, as well as obesity) associated with drug deaths in Maine. Many of the physical conditions might diminish respiratory capacity or otherwise affect the body’s ability to maintain homeostasis under pharmaceutical stress. Adverse reactions associated with legitimate medications or illicit drugs, on their own or via interaction with methadone, also might have played a role in mortality. This exemplifies the many factors that may be important in accurately attributing cause of death.

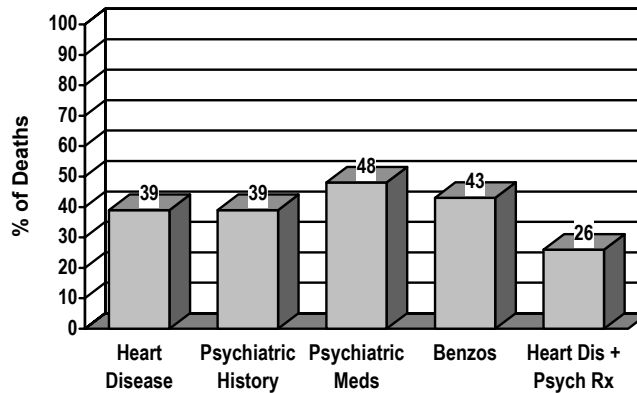


Figure 14: Examination of 23 methadone-associated death cases in Cumberland County, Maine (data from Sorg 2002).

Florida. 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 November 2002, the Florida Department of Law Enforcement (FDLE) issued a report on 2,657 toxicology investigations from the Medical Examiners Commission, covering January through June 2002 and representing 3.0 percent of the total 87,500 deaths in the State during that 6-month period (FDLE 2002). A variety of drugs were noted, with increased prevalence of *both* lethal and non-lethal levels (in undefined amounts) noted for benzodiazepines (2 percent), cocaine (4 percent), oxycodone (7

percent), hydrocodone (19 percent), and methadone (31 percent), compared with the prior 6-month period. Heroin-related deaths declined 15 percent in the same period.

Significantly, in examining only lethal cases, methadone was the only agent that showed an increased prevalence (36 percent) from July-December 2001 to January-June 2002. Of the 254 statewide methadone-associated deaths during the first six months of 2002, nearly three-quarters (73 percent) were classified as accidental. Approximately 17 percent were with methadone as the sole agent and 83 percent were in combination with other drugs; however, determinations of methadone as a causative agent versus merely “present” were somewhat equivalent (see *Table 3*). Suspected sources of methadone were not reported.

Table 3: Florida Methadone Deaths January - June 2002			
	Cause	Present	Total
Methadone Only	23	21	44
Methadone+Others	110	100	210
Total	133	121	254

North Carolina. 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. 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 2002).

The number of deaths attributed to methadone as a *sole agent* increased more than eight-fold during the five-year period, from 7 in 1997 to 58 in 2001, or from 6 percent to 26 percent of all single agent deaths during those years (see *Figure 15*). There also was

an increase during 1999 to 2001 for methadone named as a component of multidrug deaths.

Figure 15.

Texas. 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. 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.

Maryland. Overall alcohol and drug-related overdose deaths in Maryland increased 16 percent between 1997 and 2001 (Lehder et al. 2002). The majority of overdoses each year were increasingly accounted for by single-drug exposures, with two-thirds of cases in 2001 attributable to such causes. The most common type of overdose either alone or in combination with another drug was broadly classified as “narcotic-related” (e.g., heroin, but not otherwise delineated).

For single-drug mentions, deaths associated with alcohol or cocaine were relatively few compared with “narcotics.” Methadone-only deaths were tracked as a separate category and, although small in number, there was a notable escalation in methadone overdose deaths from 2 in 1997 to 21 in 2001, with the greatest increase from 5 to 14 methadone cases between 1999 and 2000 (*Figure 16*).

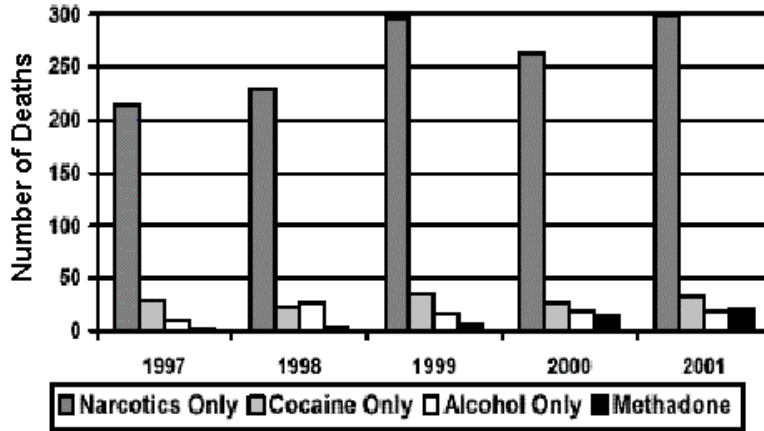


Figure 16: Number of single-drug overdose deaths by year in Maryland (Lehder et al. 2002).

Total overdose deaths increased 16 percent during the 5-year period (from 482 to 559), while the proportion of single-drug methadone-related deaths rose 10-fold from 0.4 to 4.0 percent of the totals. Influences behind the increases in methadone cases, such as source of the drug, were undetermined due to insufficient information.

During the 5-year period, males outnumbered females in overdose deaths, although numbers of females were increasing; for example, rising from 14 percent of the total in 1997 to 21 percent in 2001. The highest proportion of deaths were in persons aged 31 to 50. Baltimore City and Central Maryland regions accounted for about 80 percent of all deaths each year, although every region in Maryland had at least one overdose per year.

Part 7. Forensic Issues

There has been concern among medical examiners and others that faulty criteria used to attribute cause of death to methadone may artificially inflate statistics and impede the ongoing development of OAT as a treatment modality (Merrill et al. 1996). For example, Roizin and colleagues (1972) have observed that evaluations of toxic drug interactions can be problematic during autopsy, and that “correlation is not synonymous with explanation”; that is, the mere presence of multiple drugs does not necessarily denote their interaction. Difficulties encountered in retrospectively evaluating drug interactions include (1) inadequate information about drug dosage, health status and pre-existing tolerance (medicobiological condition) of the subject; (2) the number of drugs taken; (3) uncertainties about drug identification and the temporal relationship between intake and adverse reactions; (4) the presence of inborn or acquired factors that are facilitating or predisposing; and (5) the body’s limited means of adaptation to adverse drug effects.

Postmortem Blood/Tissue Analyses

Serum methadone levels (SMLs) considered as therapeutic during OAT commonly overlap those reported in methadone-associated deaths (Milroy and Forrest 2000; Sorg 2002). In review articles, methadone postmortem concentrations observed as fatal by various authors have ranged from 60 to 4,500 ng/mL (Mikolaenko et al. 2002; Wolff 2002; also see *Appendix C* for factors used in converting reported measures to ng/mL). In one study, Caplan et al. (1983) reported several overlapping methadone concentration ranges found post-mortem: 70 to 1,400 ng/mL in methadone-only deaths (n=18); 100 to 1,400 ng/mL in polydrug-related deaths with methadone as one agent (n=16), and 50 to 3,400 ng/mL in non-drug-related deaths that found methadone present (n=43). While some pathologists regard an SML greater than 400 ng/mL sufficient to cause death, even in persons tolerant to opioids (Merrill et al. 1996), this is at odds with established recommendations for effective OAT, in which SMLs should be kept within a trough range of 150-600 ng/mL or optimally at about 400 ng/mL for most patients, with peak levels being two-fold greater. In view of the high degree of overlap between therapeutic and putatively fatal methadone serum levels, Segal and Catherman (1974) long ago questioned whether “overdose” was a properly descriptive term in association with

fatalities and proposed “adverse reaction to narcotic drugs” as a substitute unless more precise pathophysiologic mechanisms could be determined and specified. More recently, it was noted that ascribing death to overdose of a particular drug also detracts attention from the possible contribution of other drugs to the cause of death (Zador et al. 1996).

Several factors may affect methadone ranges found in fatalities: low or lost opioid tolerance; slower or altered opioid metabolism; interactions with other drugs; and even antibodies to methadone in certain persons. Furthermore, it would be necessary to consider time of death in relation to oral ingestion (peak levels expected at 2-4 hours) and the possibility of postmortem redistribution of methadone (Karch and Stephens 2000; Sorg 2002; Wolff 2002). Milroy and Forrest (2000) analyzed 111 fatalities in which methadone was mentioned, with methadone poisoning given as sole cause of death in 55 cases. Average methadone concentration in these deaths was 584 ng/mL (range 84-2700 ng/mL) in whole blood; similarly, mean concentration in 56 cases ascribed to methadone in combination with other drugs was 576 ng/mL (range 49-2440 ng/mL) in whole blood. However, they note that the ratio of plasma to whole blood in antemortem samples is 1:1.3, and applying this conversion factor to postmortem whole blood samples would result in about 23 percent lower *serum level* values prior to death, which underscores the difficulties of attempting to interpret the lethality of postmortem drug concentrations in whole blood using parameters of acceptable serum levels in the living. Of further importance, when multisite blood sampling was performed by these researchers, there was up to a 100 percent discrepancy in concentrations of methadone, and other drugs, taken from different sites in the same body. These and other authors (Karch and Stephens 2000; Prouty and Anderson 1990) have noted that a degree of caution must be exercised in determining fatal drug concentrations due to the phenomenon of postmortem redistribution.

Postmortem movement of methadone from other tissues (e.g., liver, stomach) into blood, and vice versa, may contribute to the problem of determining accurate concentrations of methadone relative to the cause of death. Concentrations of drugs in postmortem blood specimens often increase with time postmortem (Prouty and Anderson 1990). Site-dependence is another confounding factor: for example, high quantities of methadone in stomach contents would indicate oral ingestion; whereas, trace or no evidence in the stomach and high serum concentrations in blood might suggest other

routes of administration (Milroy and Forrest 2000; Robinson and Williams 1971). Further, Drasch and colleagues (2000) noted a marked increase of the R-methadone enantiomer in fatal cases, suggesting selectively and detrimentally slow metabolism of this component in certain persons or circumstances. Drasch and colleagues, as well as Karch and Stephens (2000), have proposed the possible need for enantioselective quantification of methadone postmortem to achieve greater forensic accuracy.

Finally, in persons engaging in polydrug abuse, methadone itself may not be sufficient to cause death; however, additive or potentiating effects of other drugs may increase methadone's lethality. Therefore, some have argued, *all* significantly measurable drugs should be included in the cause of death investigation (Milroy and Forrest 2000).

Death Classification Schemes

Defining methadone-associated deaths is complicated by problems of inconsistency among forensic authorities in determining and recording information surrounding the fatalities. This is further burdened by the complexity of classification schemes that are subject to interpretation or vaguely elaborated to begin with, as in many of the epidemiological reports. At the least, a suitable case definition would involve a multifaceted approach taking into account a matrix of factors (as shown in **Table 1**, above). Factors critical for prevention would include the form of methadone (solid versus liquid) ingested and its source (legitimate or illegitimate); although, the difficulties in making such determinations must be recognized and overcome.

Currently, the reporting and classification of deaths involving drugs in the U.S. is closely tied into the death registration system (Fingerhut and Cox 1998; Hanzlick 1997). All States have a standard death certificate based on a model form called the "U.S. Standard Certificate of Death." A manner-of-death classification and cause-of-death section, which also includes details about the circumstances surrounding death, are completed by the certifier of death, whether a physician, medical examiner, or coroner (Hanzlick et al. 2002). Cause and manner of death are essentially opinions, requiring the educated and informed judgment of the certifier but supported by substantive evidence. There are five options in most States for manner-of-death classification: (1) natural, (2) accidental, (3) suicide, (4) homicide, and (5) undetermined (or "could not be

determined”). This scheme was an American invention, added in 1910 to death certificates, for helping to clarify the circumstances of death and further assist in coding cause-of-death information; it is not addressed directly by World Health Organization classifications (Hanzlick et al. 2002). Most opioid poisoning or overdose deaths might be classified as accidental, unless there was evidence of *intent* to harm oneself (suicide) or another person (homicide). However, there are many gray areas of interpretation, such as determining whether a drug exposure was acute (suggesting an accident) or more chronic (possibly connoting death due to nature causes, even if there was recent drug abuse).

Intentionality – the motivation or purpose behind drug use – also is difficult to determine; for example, was a person taking excessive amounts of opioid medication attempting to achieve euphoric effects, quell an acute exacerbation of pain, or commit suicide? As a further consideration, one author noted that it is difficult to analyze mortality by a specific drug or even drug class when using death certificate information, since many cases fall into “other, mixed, or unspecified” drug categories. (Kallan 1998).

Death certificate information is passed from local authorities to the State, and from the States to the national level. The U.S. follows World Health Organization procedures for documenting death, and the coding of causes is usually done at the State level following the latest version of the International Classification of Diseases (currently ICD-10 [NCHS 2002; van Laar et al. 2002]). These data is submitted to the custodian of U.S. mortality data, which is the National Center for Health Statistics (NCHS) within the Centers for Disease Control and Prevention (CDC). Annual national mortality data reports usually lag about two years behind the current calendar year (Hanzlick 1997).

Up to 20 causes of death, if reported, can be coded from a single death certificate (Fingerhut and Cox 1998), so the need for death certifiers to supply complete and accurate information and for nosologists to be meticulous in their coding is apparent. However, Hanzlick (1997) has noted that causes of death are sometimes reported nonspecifically or incompletely, and even yes/no questions on death certificates – e.g., “Was an autopsy performed?” – have been inaccurately reported.

The 9th Edition of the International Classification of Diseases (ICD-9; WHO, 1979) is the version used from 1979 until fairly recently, with 10th Edition (ICD-10) finding use during 1999-2000 in most countries. The ICD-9 contains two sets of codes for classifying

poisoning deaths: external cause of death (E-codes) and diagnosis codes. E-codes, of which there are 114, specify both the intent (e.g., unintentional, suicide, homicide) and the drug-class causing the poisoning: for example, unintentional poisoning by opiates and related narcotics. Diagnosis codes are used to add specificity to the cause, also naming a specific agent, but never used to code the underlying intent of death (Fingerhut and Cox 1998). ICD-10 adopted an alphanumeric system, so codes differ from those in ICD-9, and blocks of codes identify deaths due to drug dependence, non-dependent substance abuse, and accidental, suicidal/self-inflicted, homicidal, and “undetermined intent” poisoning. The most frequently abused drugs are grouped together, rather than by therapeutic class, and secondary codes allow each substance to be further identified. Methadone, which was not specifically categorized in ICD-9, was specifically added to ICD-10 (Flanagan and Rooney 2002; van Laar et al. 2002). As can be imagined, with so many classification codes, which must be based on the limited information provided in death certificates – and also subject to human errors in completeness, interpretation, coding, or keying – there is a high potential for inconsistencies, inaccuracies, and some confusion (Kung et al. 2001).

Numerous studies of methadone-associated mortality have gone beyond death certificate information to include meticulous surveys and examinations of decedents’ medical treatment records and/or death-certifier investigations (such as, autopsy and toxicology reports). Some of these studies are listed in *Appendix B*. Unfortunately, comparisons of studies are hampered by a lack of common terminology and case definitions. Some authors have made the semantic distinction that methadone-associated deaths are cases in which methadone is present but not causative; whereas, methadone-related deaths are those in which methadone contributes directly to the death process in some way (CDHAG 2000). One researcher proposed a three-tiered hierarchy of fatalities involving methadone, distinguishing between: (1) *methadone detected* – in which methadone is found at autopsy irrespective of cause of death; (2) *methadone related* – in which methadone is detected and cause of death also is found to be drug-related; c) *methadone caused* – in which methadone is the sole agent in a drug-related death (Zador in CDHAG 2000, p 29). However, causation in this scheme could be erroneously attributed, since many other factors might play more pivotal roles and methadone’s influence could be entirely benign even as a sole agent. Hence, these subtleties of

definition appear unhelpful, unless the terms are more fully defined and universally understood and accepted by nosologists.

Cone et al. (2003) recently proposed a different scheme for reporting and evaluating drug-associated mortality data. Their objective was to more carefully determine the roles of oxycodone and the specific drug product OxyContin® in deaths from 1999 to 2002. They found that most of the evaluated deaths involving the two drugs (90.6 percent) were related to drug abuse and that the vast majority (96.7 percent) were associated with the ingestion of multiple drugs, thus highlighting the need to consider the influence of polydrug abuse when determining cause of death and to avoid prematurely attributing culpability to any one agent. Only 30 of 919 drug abuse deaths involved oxycodone alone, and only 40 percent of those (12/30) specifically involved OxyContin.

Cone and colleagues developed their categorization scheme using terminology from SAMHSA's Drug Abuse Warning Network (DAWN). Thus, "drug abuse" is defined as the non-medical use of a substance for psychic effect, dependence, or suicide attempt. "Drug-induced death" is a fatality resulting directly from drug abuse, such as drug overdose or the interactive effects of drug combinations. "Drug-related death" is a fatality in which abuse of a drug (or drugs) is a contributing factor, but is not the sole cause of death. Fatalities are further delineated as involving either a single drug or multiple drugs. Using these definitions, the researchers disaggregated mortality cases into one of 11 groups for analysis (*Figure 17*). This particular study was complicated by the investigators' goal of specifically assessing the possible involvement of the OxyContin product – distinguishing it from oxycodone in general – and by the fact that their analysis included the tracking of demographic data and each of the other drugs involved in multidrug cases. Of interest, methadone was ranked 18th among the top 20 co-abused drugs, being mentioned in about 6 percent (52/889) of fatalities involving multiple drugs, yet it comprised only 0.7 percent of U.S. analgesic prescriptions in 2001, according to the authors (based on IMS data). This might suggest that most of the methadone found in these individuals was diverted, but further investigation is required. Cone and colleagues concluded that the use of standardized terminology and a group classification scheme, such as the one based on the DAWN system, would enhance future evaluations of opioid involvement in drug abuse deaths and allow for more meaningful comparisons across studies.

Categorization of Case Reports in the Oxycodone Postmortem Database	
Group	Description
0	Incomplete; case lacked autopsy report or COD statement, or lacked specific toxicology results
1	No oxycodone identified by toxicology tests specific for oxycodone
2	Death was unrelated to drug abuse, e.g., cancer death
3	OxyContin was identified by evidence at the scene, credible witness, or by analysis of stomach contents; other contributory drugs were identified by toxicology tests; death was drug-induced
4	Oxycodone was identified by toxicology tests; no evidence of OxyContin; death was drug-induced
5	OxyContin was identified; other contributory drugs were identified by toxicology tests; death was drug-related
6	Oxycodone was identified by toxicology tests; no evidence of OxyContin; other contributory drugs were identified by toxicology tests; death was drug-related
7	OxyContin was identified; no other contributory drugs were identified by toxicology tests; death was drug-induced
8	Oxycodone was identified by toxicology tests; no evidence of OxyContin; no other contributory drugs were identified by toxicology tests; death was drug-induced
9	OxyContin was identified; no other contributory drugs were identified by toxicology tests; death was drug-related
10	Oxycodone was identified by toxicology tests; no evidence of OxyContin; no other contributory drugs were identified by toxicology tests; death was drug-related

Figure 17: Scheme for evaluating oxycodone/OxyContin fatalities (Cone et al. 2003).

A long-established approach for tracking medication-associated problems and deaths in the U.S. is *MedWatch*, the FDA’s Safety Information and Adverse Event Reporting Program. This is a voluntary reporting system for gathering clinical information about all safety issues involving medical products, including prescription and over-the-counter drugs, biologics, and special nutritional products. MedWatch allows manufacturers, healthcare professionals, and consumers to report serious problems (including deaths) that they suspect are associated with the drugs and medical devices they make, prescribe, dispense, or use.

Reporting typically is done by mail or fax, using the multipurpose MedWatch 3500 form (see *Appendix D*). The system relies on the reporter’s ability to gather accurate and comprehensive information and his or her expertise in attributing the event to the drug(s) or product(s) in question.

Another voluntary reporting system for gathering and evaluating data on deaths attributed to toxicity and/or poisoning is the Pediatric Toxicology (PedTox) Registry[®] sponsored by the National Association of Medical Examiners (NAME) (*Appendix E*). This focuses on children age 12 and under (including infants) who were determined to have died from the toxic effects of a drug or poison. A relatively simple reporting form is used for submitting data to a designated custodian. In addition to standard death certificate entries on manner and cause of death, several other practical areas of useful information are probed, including demographics. Five categories are used to depict the suspected *role* of the involved agent(s) to help assess causality. The accumulated data are evaluated and reported in two sections – a case description database and summaries by substance – which are accessible at the NAME web site (http://www.thename.org/pedtox_index.htm) by registered members. Although this approach targets a specific age group and is broad-based in terms of the agents of interest, the model appears useful for gathering qualitative and quantitative intelligence data on fatalities involving particular substances.

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Part 9. Appendices

Appendix A. Epidemiologic Databases Consulted

Appendix B. Past Investigations of Methadone-Associated Mortality

Appendix C. Methadone Serum Level Conversion Factors

Appendix D. MedWatch Form

Appendix E. PedTox Case Report Form (from NAME)

Appendix F. Methadone Identified in Laboratory Testing

Databases Containing Information Relevant to Opioid Prescribing, Use, Abuse, Overdose/Poisonings, and Fatalities <i>(Web site URLs indicated where available)</i>	
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 ARCOS	U.S. Drug Enforcement Administration Automation of Reports and Consolidated Orders System (ARCOS) from the DEA. The Controlled Substances Act of 1970 (§ 827) created the requirement for Manufacturers and Distributors to report their controlled substances transactions to the Attorney General. The Attorney General delegates this authority to the Drug Enforcement Administration (DEA). ARCOS is an automated, comprehensive drug reporting system which monitors the flow of DEA controlled substances from their point of manufacture through commercial distribution channels to point of sale or distribution at the dispensing/retail level – 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	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 National Drug Control Strategy	White House Office of National Drug Control Policy Annual report to Congress draws data from a variety of sources relating to drug misuse in the U.S. to present past and current trends, as well as the government's planned strategies and budgets for dealing with the problems. See http://www.whitehousedrugpolicy.gov/index.html .
DENS	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 as abused in addiction treatment programs. See http://www.densonline.org/ for more information.

Databases Containing Information Relevant to Opioid Prescribing, Use, Abuse, Overdose/Poisonings, and Fatalities (Web site URLs indicated where available)	
FDA MedWatch	U.S. Food & Drug Administration MedWatch, the FDA Safety Information and Adverse Event Reporting Program, serves both healthcare professionals and the medical product-using 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 NAMCS	National Center for Health Statistics / Centers for Disease Control & Prevention See: http://www.cdc.gov/nchs/about/major/ahcd/ahcd1.htm The National Ambulatory Medical Care Survey (NAMCS) is designed to meet the need for objective, reliable information about the provision and 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) is designed to collect 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 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 TESS	American Association of Poison Control Centers 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 solutions to the pharmaceutical and healthcare industries, offering business intelligence products and services including marketing data on prescription and over-the-counter pharmaceutical products. IMS tracks and measure 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 (Web site URLs indicated where available)	
RADARS	<p>On June 27, 2002, Purdue Pharma announced establishment of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS™) System, an initiative to study the prevalence of abuse and diversion of controlled prescription medications. The system is designed to obtain quantitative and qualitative information on the relative rates of abuse, addiction, and diversion of commonly prescribed prescription pain medicines.</p> <p>Initially, the RADARS System was to monitor six types of prescription opioid pain medications with recognized abuse potential: morphine, buprenorphine, fentanyl, hydrocodone, hydromorphone, and oxycodone. Data collection was expected to be completed during fall or early winter of 2002. As experience with the System accumulates, other types of medications, such as benzodiazepines (alprazolam and diazepam), would be added. Database is not open to the public.</p> <p>See: http://www.purduepharma.com.</p>
OTHER...	
NVDRS	National Violent Death Reporting System (NVDRS) is a recent State-based initiative funded by the CDC that 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	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/NISS	Consumer Product Safety Commission (CPSC) uses death certificate data for a National Injury Surveillance System (NISS). 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 initiated by many States to provide data for public health initiatives, law enforcement, and the promotion of early intervention and prevention of drug-related problems. PMPs rely on pharmacies and other drug dispensers to send data electronically to central 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/

Access to all web sites verified in April 2003

Appendix B. Past Investigations of Methadone-Associated Mortality

Epidemiologic / Descriptive Studies of Methadone-Associated Mortality <i>(listed by latest year of data collection; may not include all studies)</i>			
Reference	Location/Date	Subjects/Design	Comments
Dole et al. 1971	New York 1960s	Series of 2 cases in methadone program.	Accidental overdose not otherwise specified.
Gardner 1970	London 1965 – 69	Descriptive study of 12 methadone deaths.	Concludes that at least 7 deaths occurred due to lack of opioid tolerance, and 8 were due to prescription of too high a starting dose (greater than 70 mg).
Baden 1970	New York 1967 – 70	Report on 24 deaths in methadone program; 8 not in OTP.	Half of methadone deaths related to abuse of alcohol and other drugs. Of 8 methadone-associated deaths outside OTP, 5 were oral overdose (2 in opioid naïve victims), 3 were IV abuse of methadone.
Gearing & Schweitzer 1974	New York 1964 – 71	Long term descriptive study on outcomes of subjects in OAT.	Reasons for the causes of death in 153 subjects not detailed, but at least 30 percent were polydrug-related.
Roizin et al. 1972	New York 1972	Series of 14 deaths, 57 percent receiving methadone.	Methadone dose range 40-180 mg/d. Polydrug abuse implicated in most cases, including morphine (4) and quinine (2).
Greene et al. 1974	District of Columbia 1970 – 73	Descriptive study of methadone death rate.	Methadone deaths increased sharply following diversion to streets – 46.2 percent of decedents were not opioid tolerant – and was curtailed sharply by restricting access to licensed clinics rather than private physicians.
Appel et al. 2000	New York 1966 – 76	176 deaths among 1,544 patients in and out of OAT program.	Overall, 93 deaths during methadone tx; 83 after leaving treatment, although rate/1,000 person years was double posttreatment. Only 2 deaths during OAT were opioid related.
Concool et al. 1979	East Harlem, NY 1969 – 76	Review of deaths in patients enrolled in OAT; risk assessment.	Mortality rate was 20 per 1000 patients, deaths largely due to alcoholism and violence. None of the deaths directly attributed to methadone.
Caplan et al. 1983	Maryland 1975 – 80	77 deaths with methadone present.	18 deaths with methadone as sole agent; overlap in serum methadone levels among sole-agent deaths, polydrug deaths, and non-drug-related deaths with methadone present.
Kringsholm et al. 1988	Denmark 1868 – 86	Descriptive study of drug deaths.	20 percent of drug deaths during abstinence were due to methadone. No details of circumstances provided.
Petry et al. 1998	New York 1975 – 86	Review of 325 deaths among OAT patients receiving methadone.	During 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 1981 – 86	Description of 25 deaths associated with methadone.	14 deaths were caused by methadone, of which 3 were in the first two weeks of starting, 6 less than two weeks after leaving OAT; 9 caused by a combination of opioids and methadone. 15 deaths were associated with benzodiazepine use.

Epidemiologic / Descriptive Studies of Methadone-Associated Mortality (listed by latest year of data collection; may not include all studies)			
Reference	Location/Date	Subjects/Design	Comments
Davoli et al. 1993	Italy 1980 – 88	Matched case control analysis of IV drug abusers in OAT.	Higher risk of overdose death for subjects who had left methadone treatment particularly within first year (Odds Ratio 7.98).
Drummer et al. 1990, 1992	Victoria, Australia 1990	10 death in methadone-treated patients.	Deaths were in early stages of OAT, dose range 45–70 mg (mean 53 mg). Six had additional CNS-active drugs present; all had chronic hepatitis; 5 had bronchopneumonia.
Kringsholm et al. 1994	Denmark 1987 – 91	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 of the victims were receiving methadone maintenance at time of death.
Neeleman and Farrell 1997	England & Wales 1974 – 92	Retrospective longitudinal survey.	Poisoning deaths involving methadone (alone or in combination) rose 80 percent per 3-year period. However, there was no evidence that this was disproportional to increases in heroin deaths.
Barrett et al. 1996	Harris County, Texas 1987 – 92	Investigation of 91 deaths involving methadone.	CDC team of investigators found 85 percent of cases involved polydrug abuse and only 20 percent of decedents were in OAT at time of death. Only 11 cases attributed directly to methadone toxicity.
La Harpe & Fryc 1995	Geneva 1987 – 93	Description of 24 deaths associated with methadone.	No deaths occurred in first two weeks of methadone tx, 3 in less than 2 weeks after leaving OAT, 11 occurred with concomitant benzodiazepines, 8 with alcohol, and 11 in presence of heroin.
Goldstein & Herrera 1995	Albuquerque 1971 – 93	Long term follow-up of 1,019 patients registered in methadone OAT.	34 percent had died over 22 years since first starting methadone; more than one-third related to drug abuse. Causes of death not provided. Subjects were 4-6 times more likely to die than non-addicts.
Clark et al. 1995	Sheffield, UK 1991 – 94	18 subjects, case study.	Reported death of 7 subjects in early stages of methadone tx, dose range 30-100 mg; 3 died after long term use, eight died from non-prescribed drug use. Multiple drug use was common but not considered to have played a major role in most deaths.
Cairns et al. 1996	Manchester 1985 – 1994	90 subjects, case study.	Showed increase in number of methadone deaths during this period; methadone was sole cause of death in 52 and 36 died from non-prescribed use. Methadone cases represented 15 percent of total fatal drug-overdoses during period.
Williamson et al. 1997	South Australia 1984 – 94	47 fatalities with risk assessment .	Widespread use of methadone tablets for chronic pain led to disproportionate increase in deaths (7 fold over use of syrup), sudden increase in deaths in 1993-94 with build up of private methadone clinics.
Caplehorn 1998	Sydney 1994	13 subjects, case study.	10 died in first two weeks during methadone induction, last dose range 25–110 mg, median 40 mg.

Epidemiologic / Descriptive Studies of Methadone-Associated Mortality <i>(listed by latest year of data collection; may not include all studies)</i>			
Reference	Location/Date	Subjects/Design	Comments
Caplehorn & Drummer 1999	Sydney 1994	Review of 86 methadone-associated deaths, risk assessment.	29 died from diversion of methadone syrup, 18 died from use of tablets, 38 died during OAT; risk of death in first 2 weeks was 6.7 times that of addicts outside OAT, but was reduced 98-fold later during methadone maintenance treatment.
Zador & Sunjic 2000	NSW Australia 1990 – 95	238 methadone-associated deaths examined.	44 percent of deaths were drug related with most (92 percent) involving polydrug abuse, and 42 percent occurred during the first week of methadone treatment.
Drummer 1997	Victoria, Australia 1994 – 97	89 deaths with methadone detected.	Toxic methadone concentrations overlapped those in non-drug-related deaths with methadone present. Those starting OAT or who used the drug occasionally were most at risk of death.
Valmana et al. 2000	London 1997	Review of 40 methadone-associated deaths	Methadone had not been prescribed in 72 percent of cases and these decedents were younger (median 22 yrs) than the prescribed-methadone victims (median 37 years), suggesting more chaotic abuse patterns in younger persons.
Perret et al. 2000	Geneva, Switzerland 1994 – 98	36 methadone cases, out of 106 total drug abuse fatalities.	Nearly all (35) had illicit drugs combined with methadone, 21 were attributed as due to methadone lethality and only a third of those decedents were in OAT. Methadone-attributed deaths remained constant at 3-5/yr throughout study period, while overall drug abuse deaths declined markedly.
Eastwood 1998	London 1998	Description of 13 childhood deaths.	13 children poisoned with methadone syrup prescribed to one or more of the opioid-dependent parents; five died. Methadone serum concentrations of deceased children overlapped those children who survived.
Karch & Stephens 2000	San Francisco 1997 – 98	38 cases (out of 3,317 examined) involving methadone.	Methadone was cited as cause of death in 21 cases, although blood methadone concentration was identical in this group and the group in whom methadone was an incidental finding.
Buster et al. 2002	Amsterdam 1986 – 98	5,200 methadone-maintained patients observed.	68 overdose deaths recorded, with a modest increase during first 2 weeks of treatment. Overall death rate was 2.3/1000 patient-years.
Heinemann et al. 2000	Hamburg, Germany 1990 – 99	Surveillance on drug-related poisonings.	Rising cases of methadone-related fatalities coincided with declines in heroin deaths. 65 percent of methadone decedents were not in an OTP.
Bartu et al. 2002	Western Australia 1993 – 99	84 methadone-related deaths evaluated.	74 percent of deaths caused by combination of drug effects, with benzodiazepines present in 3/4 of those cases. 57 percent were not in an OTP at time of death. Methadone-associated mortality peaked in 1998 at 7.7/1000 patients treated, one year after expansion into the private sector.

Epidemiologic / Descriptive Studies of Methadone-Associated Mortality <i>(listed by latest year of data collection; may not include all studies)</i>			
Reference	Location/Date	Subjects/Design	Comments
Green et al. 2000	South Australia 1996 – 99	35 cases of methadone causing or contributing to death.	10 victims were receiving methadone maintenance tx, of whom 4 died within first week. Eight non-OAT cases involved diverted methadone, with 7 including other drugs. Mean age of decedents was 25 years.
Oliver et al. 2002	Sheffield, UK 1997 – 99	82 drug-abuse related deaths	Deaths attributed wholly or partially to methadone declined from 37 percent to 18 percent during the 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 despite 18 percent increases in methadone prescriptions since that year. 45 percent of deaths involved persons not prescribed methadone, all but 2 involved drug abuse-related causes, none in persons within one month of starting methadone maintenance. Of those on methadone prescription, 60 percent were on observed dosing at time of death.

Appendix C. Methadone Serum Level Conversion Factors

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

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

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

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

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

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

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

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

Appendix D. MedWatch Form

U.S. Department of Health and Human Services		Form Approved: OMB No. 0920-0000 Expires 02/28/06 See OMB instructions on reverse	
MEDWATCH		For VOLUNTARY reporting of adverse events and product problems	
The FDA Safety Information and Adverse Event Reporting Program		Page _____ of _____	
A. Patient information		C. Suspect medication(s)	
1. Patient identifier <small>In confidence</small>	2. Age at time of event: or Date of birth:	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight ____ lbs or ____ kgs
B. Adverse event or product problem		D. Suspect medical device	
1. <input type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)		1. Brand name	
2. Outcomes attributed to adverse event (check all that apply) <input type="checkbox"/> death (include yr) <input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalization - initial or prolonged		2. Type of device	
<input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage <input type="checkbox"/> other: _____		3. Manufacturer name & address	
3. Date of event (month/yr)	4. Date of this report (month/yr)	4. Operator of device <input type="checkbox"/> health professional <input type="checkbox"/> lay user/patient <input type="checkbox"/> other: _____	
5. Describe event or problem		5. Expiration date (month/yr)	
		7. If implanted, give date (month/yr)	
6. Relevant tests/laboratory data, including dates		8. If explanted, give date (month/yr)	
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatohepatic dysfunction, etc.)		9. Device available for evaluation? (Do not send to FDA) <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> returned to manufacturer on _____ (month/yr)	
		10. Concomitant medical products and therapy dates (exclude treatment of event)	
8. Concomitant medical products and therapy dates (exclude treatment of event)		E. Reporter (see confidentiality section on back)	
		1. Name & address	
9. Health professional? <input type="checkbox"/> yes <input type="checkbox"/> no		3. Occupation	
10. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. <input type="checkbox"/>		4. Also reported to <input type="checkbox"/> manufacturer <input type="checkbox"/> user facility <input type="checkbox"/> distributor	

PLEASE TYPE OR USE BLACK INK

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

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

Appendix E. PedTox Case Report Form (from NAME)

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

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

Your name, office, phone, e-mail _____			

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

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

Appendix F. Methadone Identified in Laboratory Testing

MEMORANDUM

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

Subject: Data on Methadone Identified in Laboratory Tests

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

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

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

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

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

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

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

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

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

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

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

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

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

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