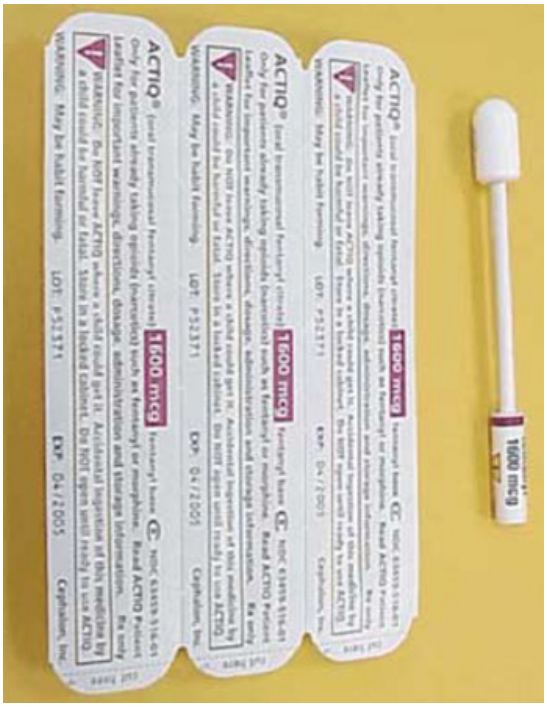
October 2013

The Fentanyl Family of Opioids

This article is the second in a continuation of the Drug Testing Matters series on opioids that was initiated in December 2011. The first four parts address information related to the opiates, and the fifth part addresses prescription drug abuse. This article and the articles to follow will present additional information on the fentanyl family of opioids and other opioids.



Introduction

Fentanyl is a well-known opioid, developed by Janssen Pharmaceuticals in 1964 as an analgesic and widely used for legitimate pharmaceutical purposes since that time. Many analogs have been synthesized and evaluated to find analgesics without the side effects of morphine. Because of the ease of synthesis and availability of precursor materials, opioids (including fentanyl and its analogs) have been used to create designer drugs for so-called "recreational" use and to circumvent legal restrictions. This article will present information on fentanyl and analogs as pharmaceuticals and will follow with information on two of the fentanyl analogs used as designer opioids.

Opioids in the fentanyl family have strong analgesia with rapid onset and short duration of effect. They are available for parenteral, oral, transdermal and transmucosal administration to treat significant pain. Phase 2 elimination times vary significantly based on the distribution and lipid solubility of the specific drug. Although safe for pharmaceutical use under proper conditions, these compounds are subject to abuse because of the number of available drugs, their strong euphoric effects, the variety of means of administration, and the relatively short detection windows.

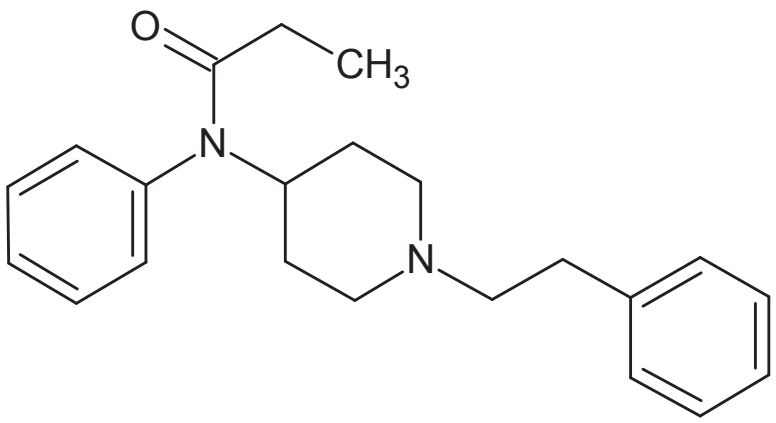
Fentanyl and some of the analogs, including designer derivatives, are much more potent than street heroin or morphine, and have resulted in many cases of acute opioid withdrawal syndrome and unintentional drug overdoses. In 2010, the Drug Abuse Warning Network reported more than 20,000 emergency department visits resulting from nonmedical use of fentanyl. (1) (This was a doubling of visits from 2004 to 2008.) In addition, the usual infectious disease problems of intravenous drug use occur. Since January 2005, the World Anti-Doping Agency has prohibited the use of fentanyl and its related substances in sports. (2) Two opioids of the fentanyl family, fentanyl and sufentanil, are widely abused by healthcare professionals. Abuse of such anesthetic agents by healthcare professionals is of great concern because of these individuals' ready access to the drugs, the high dependence potential, and the serious consequences.

The Fentanyl Family: Pharmaceutical Use

The information on metabolites below is from Baselt (3), Thevis (4), and Skulska. (5)

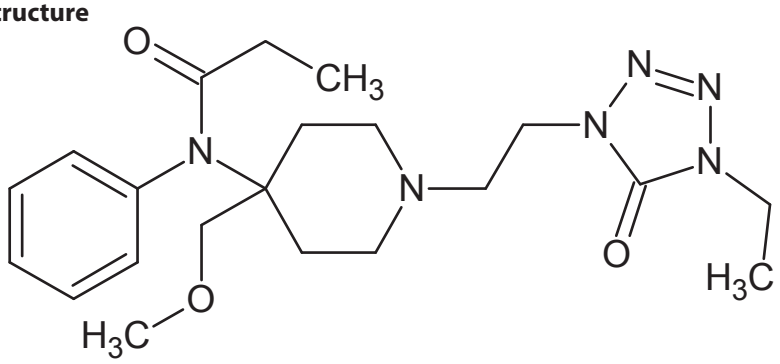
1. **Fentanyl** [Controlled Substances Act (CSA) Schedule II] is marketed under a number of trade names such as Duragesic (Janssen Pharmaceuticals) and Actiq (Cephalon, Inc.) and is used as an analgesic, an adjunct to general anesthesia, and as a respiratory depressant. Fentanyl has about 100 times the potency of heroin and may be administered parenterally, intranasally, orally by lozenges, or transdermally by patches. Doses vary markedly depending on the technique and the patient. Fentanyl is more lipid soluble than morphine and has a rapid onset of action; however, the elimination half-life is long because of rapid redistribution. Up to 85% of an IV dose of fentanyl is excreted in the urine over a 3- to 4-day period. Very little unchanged drug is present in urine. Oxidative dealkylation removes a phenylethyl group and produces norfentanyl as a major metabolite that makes up from 26% to 55% of the excreted material. Other hydroxylated metabolites (e.g., omega-hydroxynorfentanyl) and despropionyl metabolites occur as well.

Fentanyl structure



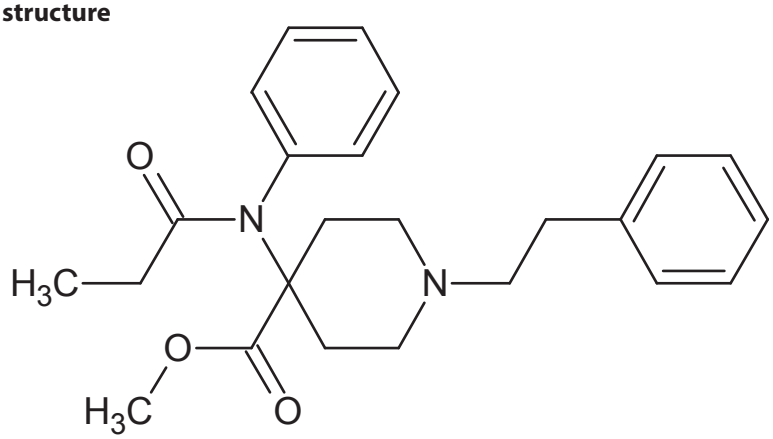
2. **Alfentanil** (CSA Schedule II) is marketed as Alfenta (Janssen Pharmaceuticals) and is a short-acting analgesic used in surgical procedures as an adjunct to general anesthesia or as a primary anesthetic. The drug is administered intravenously as the hydrochloride with a peak effect being seen in 2 minutes, with analgesia lasting about 10 minutes. Alfentanil is essentially completely metabolized. In a 24-hour urine, less than 1% of the parent drug appears, while about 31% appears as noralfentanil and 16% appears as free and conjugated O-demethylnoralfentanil. Other minor metabolic products make up the remainder of excreted material.

Alfentanil structure



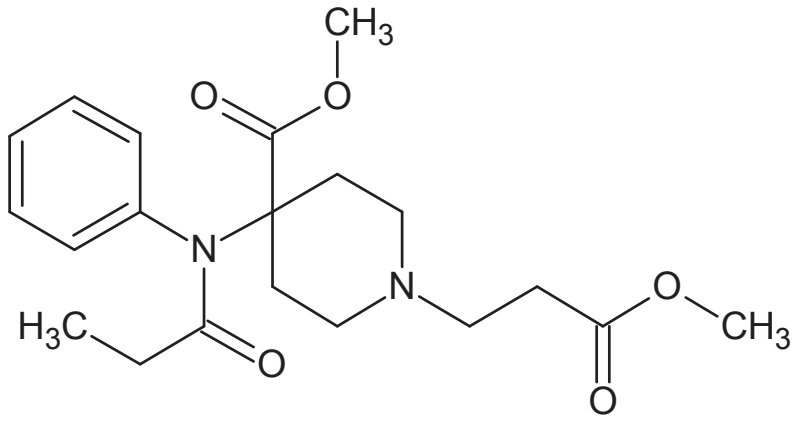
3. **Carfentanil** (CSA Schedule II) is marketed as Wildnil. Carfentanil has a potency about 9,000 times that of morphine and 100 times that of fentanyl, and has an extremely rapid onset of symptoms. Carfentanil is only authorized for use by veterinarians certified to use the drug for tranquilizing large animals (e.g., bear, elk, elephants). Carfentanil is not approved for use in humans. (6) The products of metabolism of carfentanil have not been clearly identified; however, pharmacokinetic modeling of carfentanil has been completed in a number of animals. Carfentanil has a half-life of 7.7 hours. (7) There have been a few instances of the inadvertent exposure of a veterinarian while using carfentanil for immobilizing an animal. A small splash of carfentanil in the eyes and mouth of a veterinarian was sufficient to produce severe opioid effects within minutes. Immediate treatment with naltrexone allowed complete recovery. (8) Following an October 26, 2002, use of an aerosol by Russian Special Forces to rescue hostages taken in a theatre, liquid chromatography/tandem mass spectrometry (LC-MSMS) was used to analyze clothing and urine from three survivors. Carfentanil and remifentanil were found on a shirt sample and norcarfentanil was found in a urine sample, probably as a metabolite of carfentanil. Because of exposure and poor medical care, 125 deaths resulted from the action. (9)

Carfentanil structure



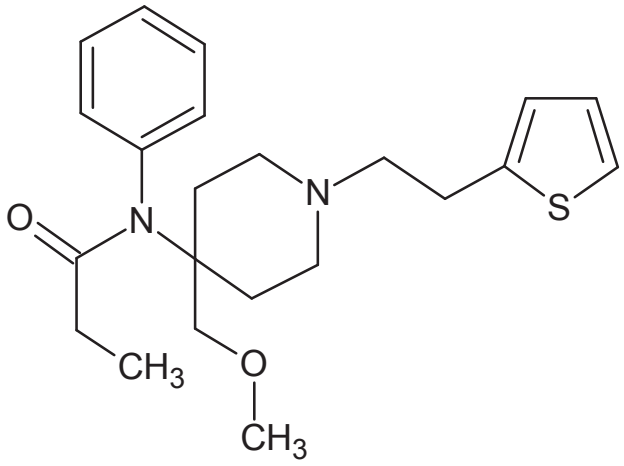
4. **Remifentanil** (CSA Schedule II) is marketed as Ultiva (Mylan, Inc.). This is a short-acting mu receptor opioid with an onset of action within 1 minute and duration of 5 to 10 minutes. The opioid is generally given by IV infusion for induction or maintenance of general anesthesia and may be used in the postoperative period or for regional or local anesthesia. The dose administered depends on the use and the patient; however, doses range from 40 to 50 ng/kg/min up to 2 mcg/kg/min. During the postoperative phase, doses are generally in the 25–200 ng/kg/min range. Product information on remifentanil indicates a three-compartment pharmacokinetic model with a rapid distribution half-life of 1 minute, a slower distribution half-life of 6 minutes, and a terminal clearance half-life of 10 to 20 minutes. (10) Remifentanil is highly bound to alpha1-acid glycoprotein in plasma. About 86% of the drug is excreted in the urine as an inactive carboxylic acid metabolite, GI-90291, along with a minor metabolite, GI-94219. Remifentanil may cross the placenta and is distributed in breast milk.

Remifentanil structure



5. **Sufentanil** (CSA Schedule II) is marketed as Sufenta (Taylor Pharmaceuticals). This opioid has a rapid onset, short duration of action, and approximately seven times the potency of fentanyl. It is used as an adjunct to primary anesthesia and as a primary anesthetic in certain cases requiring assisted ventilation. As noted earlier, this drug is widely abused by healthcare professionals. It is highly lipid soluble, about 90% plasma protein bound, and has an elimination half-life of about 2.5 hours, which is between that of fentanyl and alfentanil. Sufentanil is usually administered by intravenous injection or infusion; however, other means such as epidural have been used.

Sufentanil structure



Sufentanil crosses the blood-brain barrier rapidly and is extensively metabolized, with 80% of a dose being excreted in the 24-hour urine. Only about 2% of the parent drug is excreted unchanged in a 24-hour urine. The primary metabolites are N-desalkylsufentanil and O-desmethylsufentanil with a significant percentage of a dose being excreted as conjugates.

The Fentanyl Family: Abuse

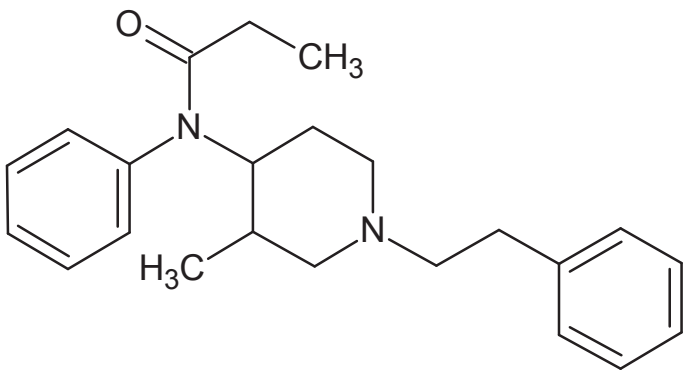
Street names of fentanyl or analogs include Apache, China Girl, Dance Fever, Friend, Jackpot, King Ivory, Poison, and Tango and Cash. Fentanyl is obtained for nonmedical use by theft, fraudulent prescriptions, and clandestine manufacture. Fentanyl patches are abused by removing the gel from the patch and injecting, ingesting, or smoking the material. Previously used patches are readily abused because a large percentage of the drug remains even after a 3-day use. When the patches are eaten or smoked in a bong, the user may get a dose that is not carefully controlled. A number of fatalities have occurred from abuse of patches. (11, 12)

Although thousands of analogs have been studied, only a few have become popular for abuse. Carroll et al. provide a list of the most commonly encountered fentanyl analogs and designer opioids. (13) The designer analogs vary primarily by various N-alkyl substitutions on the piperidine ring, addition of a methyl group at the 3-position of the piperidine, and by addition of an alkyl group at the 4-position of the piperidine (along with the propionamide). Of these, the methylfentanyls and analogs are of particular concern because of the low minimum lethal dose and the narrow range between an effective dose and a lethal dose. The methylated analogs tend to produce more analgesia than euphoria, but the euphoria effect is longer than for heroin. (14)

The various methylated analogs of fentanyl have been known as "China White." This is something of a misnomer because the name initially applied to highly purified heroin from Southeast Asia. (15) The more frequently abused designer opioids are 3-methylfentanyl and alpha-methylfentanyl:

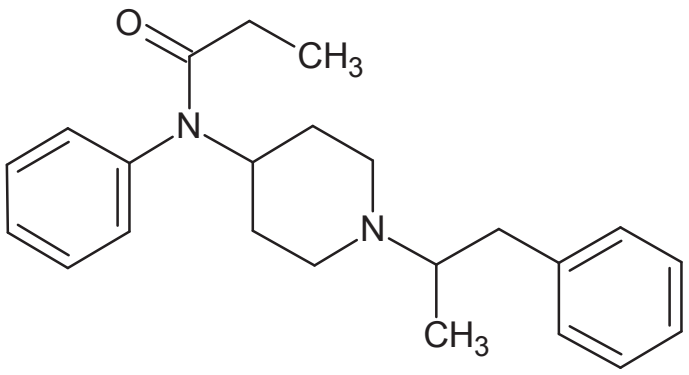
1. **3-methylfentanyl** (CSA Schedule I) is a street drug that has potency many times that of fentanyl and about 6,000 times that of morphine. (16) Meyer et al. identified a number of metabolites in rats using LC coupled with linear ion trap-mass spectrometry (LC-MS). (17) A variety of nor-alkyl and hydroxylated Phase I metabolites are produced. Phase II metabolites are generally glucuronides. In addition, there are a number of analogs and enantiomers of 3-methylfentanyl which bind to the mu receptor and demonstrate that stereochemistry may be important in the design of specific ligands. (18)

3-methylfentanyl structure



2. **Alpha-methylfentanyl** has a minimum lethal dose of 125 micrograms. (19) A number of metabolites have been identified in rats. The major metabolites include norfentanyl and omega hydroxypropionylnorfentanyl. Because these are also metabolites of fentanyl, other minor metabolites may be used to identify the parent drug. Examples include para-hydroxy alpha-methylfentanyl and omega- and omega-1-hydroxypropionyl alpha-methylfentanyl. (20)

Alpha-methylfentanyl structure



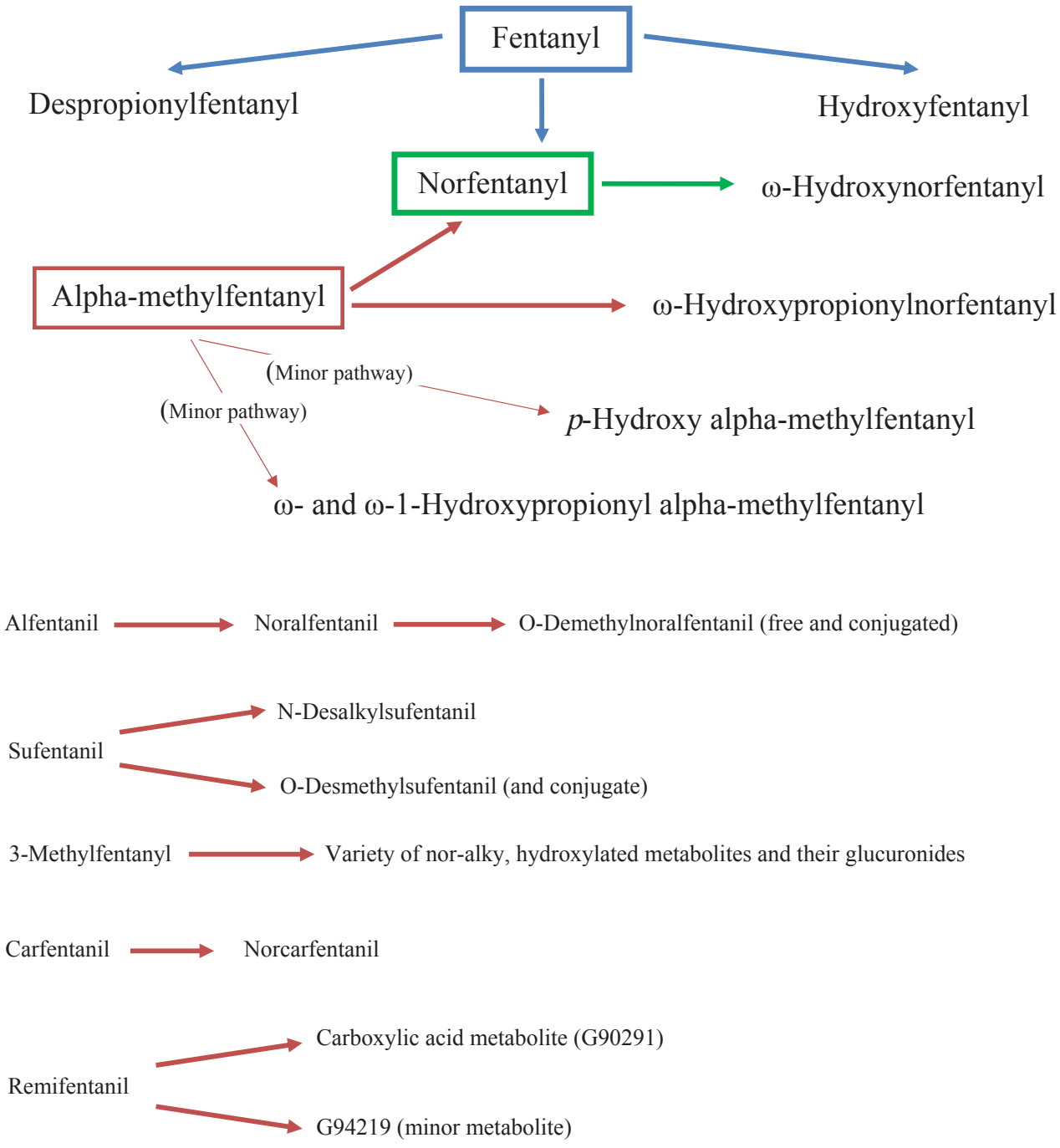
Identifying members of the fentanyl family of opioids is a challenge because there are common basic structures. Even though little of the parent drug is excreted in most cases, the intact drug molecule may be essential for identification of the drug used. Papers listed in the references include methods for identification of the various opioids of the fentanyl family.

The growth of the designer drug industry prompted the Federal Controlled Substance Analogue Enforcement Act in 1986. (22) This statute establishes that a "controlled substance analog shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in Schedule I." As a result, the Drug Enforcement Agency (DEA) has the authority to take action to control designer drugs of the opioid family.

In 2007, the DEA regulated the fentanyl precursor N-phenylethyl-4-piperidone, which has resulted in the reduction of the clandestine synthesis of the opioids. The abuse of designer drugs of the fentanyl family has also declined because of both the legal restrictions and the availability of heroin; however, in the case of a limited supply of heroin, the abuse of the fentanyl analogs may increase. Clandestine synthesis of this class of drugs fails to provide purity information or toxicological testing, leaving testing to be done on seized drugs and the drug users.

In one study to identify 25 opioids, samples were extracted with butyl acetate and separated by LC on a Genesis C(18) reversed-phase column by a gradient consisting of acetonitrile and ammonium acetate at pH 3.2. (21) The mass spectrometric analysis was performed with a quadrupole-linear ion-trap mass spectrometer equipped with a turbo ion spray interface in the positive ion mode using multiple reaction monitoring. Quantification was performed based on five isotope-labeled internal standards. The limits of quantification were adequate for screening and quantification of opioid drugs at low therapeutic or abuse concentration levels.

Fentanyl Family Metabolism



Note: This diagram shows major metabolic pathways and does not show all conjugated metabolites.

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Richard Hilderbrand, Ph.D., has more than 40 years of experience in the field of biochemistry, which includes the toxicology of drugs and other substances in humans and testing for drugs of abuse and performance-enhancing substances. He has overseen and directed drug testing programs for the U.S. Navy, the Department of Defense, and the Substance Abuse and Mental Health Services Administration. He has worked in drug testing laboratories accredited by all those agencies, including serving as the Responsible Person of a Department of Health and Human Services–certified laboratory. In addition, he worked at the U.S. Anti-Doping Agency in doping control programs and at a doping control laboratory at UCLA. He is the author of one book, seven book chapters, 11 peer reviewed articles and numerous reports and presentations concerning testing of biological specimens. He is currently retired and serves as a consultant to and inspector for the National Laboratory Certification Program.