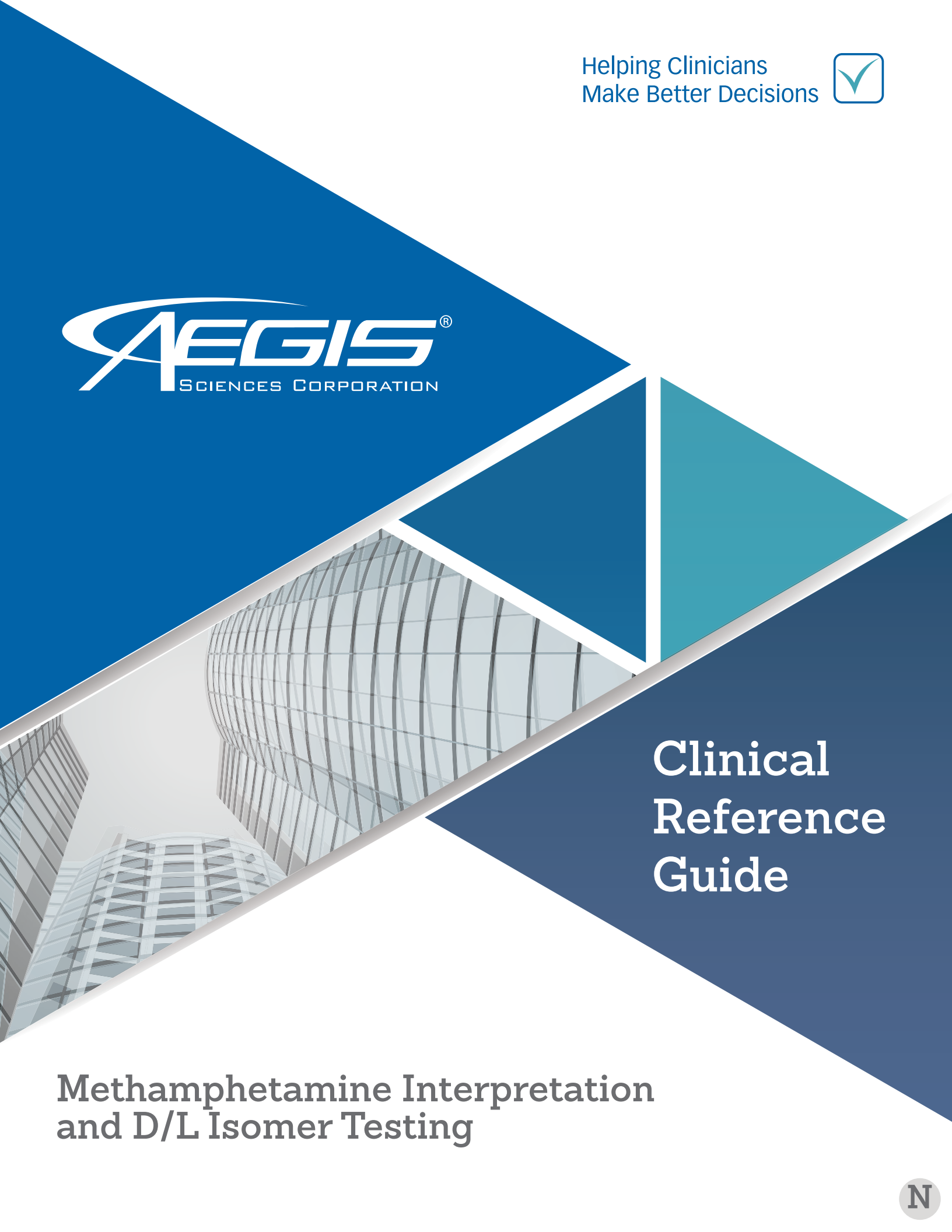


Helping Clinicians  
Make Better Decisions



# Clinical Reference Guide

## Methamphetamine Interpretation and D/L Isomer Testing

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Understanding each scenario involving either licit or illicit sources of exposure that may lead to a positive methamphetamine result is important to patient care. Results of specialized isomer testing can aid in determination of the potential cause of a positive methamphetamine result.

### A. Methamphetamine and Cross-Reactivity

Immunoassays, which are commonly used as a first step for urine drug testing, exhibit variable cross-reactivity to pseudoephedrine and other over-the-counter (OTC) products. When immunoassays are used at the point-of-care, false positives may commonly occur, and follow-up definitive testing may be appropriate. The pitfalls of cross-reactivity are bypassed with current techniques of definitive testing by gas chromatography/mass spectrometry (GC/MS) or liquid chromatography/tandem mass spectrometry (LC/MS/MS); therefore, any Aegis healthcare report that includes methamphetamine will rule out pseudoephedrine use or other cross-reacting substances. A list of prescription and nonprescription drugs in the U.S. that could potentially result in a positive result for methamphetamine on an Aegis report can be found in Table 14.1. An isomer test may be ordered to assist in further differentiating the potential cause of a positive result.<sup>1,2</sup>

Of note, certain substances have previously been available outside of the U.S., such as famprofazone, dimethylamphetamine, fencamine, and furfenorex, which could cause a positive methamphetamine result.<sup>3</sup> It is also worth noting that methamphetamine has been detected as an adulterant of other illicit substances.<sup>4</sup>

Table 14.1: Methamphetamine Testing by Mass Spectrometry

DRUGS POTENTIALLY RESPONSIBLE	DRUGS NOT RESPONSIBLE
Methamphetamine (Desoxyn®)	Pseudoephedrine
Benzphetamine	Amphetamine
Illicit Methamphetamine	Dextroamphetamine
Selegiline (EMSAM®, Zelapar®)	Other OTC or prescription medications
OTC vapoinhaler containing levmetamfetamine	

Methamphetamine is metabolized to amphetamine, but the reverse does not occur. Consequently,

use of amphetamine products (e.g., Adderall®, dextroamphetamine) does not typically result in a positive result for methamphetamine when definitive testing is used.<sup>1</sup> The one exception is when a very low concentration of methamphetamine is detected in the presence of a high concentration of amphetamine. Researchers have proposed that methamphetamine may be present in pharmaceutical preparations of amphetamine (including Adderall® and Vyvanse®) as a pharmaceutical impurity, with methamphetamine being present in urine at 0.5% or less of the amphetamine concentration.<sup>5,6</sup>

### B. Methamphetamine *d*- and *l*-isomers

Methamphetamine exists as two optical isomers (enantiomers) that are designated as *d*- and *l*-isomers. The *d*-form has a strong stimulant effect on the central nervous system (CNS) and high misuse potential, while the *l*-form in therapeutic doses has primarily peripheral activity.

Illicit methamphetamine may contain either or both isomers, although concentrations of the *d*-isomer are often detected in the absence of or at concentrations greater than *l*-methamphetamine.<sup>7</sup> In a review of positive methamphetamine results from over 2,300 urine specimens submitted to Aegis from April 1 to June 30, 2017, 92% of specimens were 100% *d*-methamphetamine, 6% contained both *d*- and *l*-isomers, and 2% were 100% *l*-methamphetamine.<sup>8</sup> The isomer prevalence depends on production method, with some methods producing higher concentrations of *l*-methamphetamine. Some Drug Enforcement Administration and state crime laboratories have reported seizures of illicit methamphetamine that contain up to 99% *l*-methamphetamine.<sup>9,10</sup> In one study, large doses of *l*-methamphetamine (0.5 mg/kg) were psychoactive after injection, but the effects of intoxication were much shorter than those experienced after *d*-methamphetamine administration. However, the effects of racemic methamphetamine (containing equal

concentrations of both isomers) were similar to those experienced after injection of *d*-methamphetamine only. Therefore, both methamphetamine isomers are subject to abuse.<sup>11</sup> Consequently, finding predominantly *l*-isomer is not a guarantee that a patient did not use illicit methamphetamine or misuse commercially available *l*-methamphetamine.

There are four prescription and OTC medications that contain or metabolize to methamphetamine. For these products, the active isomer should be pure (100%); however, up to a 5% impurity of the alternative isomer is a prudent consideration when interpreting results. The non-stimulant *l*-methamphetamine is the active ingredient (levmetamfetamine) in some OTC nasal decongestant inhalers and a metabolite of the prescription medication selegiline, a monoamine oxidase inhibitor. This latter medication was originally developed for the treatment of Parkinson's disease, but certain formulations are also utilized in the treatment of depression. These sources of methamphetamine are expected to be comprised of 100% *l*-methamphetamine ( $\geq 95\%$ ) and will be excreted as such.

Stimulant *d*-methamphetamine is the active ingredient in the schedule C-II medication, methamphetamine (Desoxyn<sup>®</sup>), a prescription medication approved for attention deficit disorder or obesity. *D*-methamphetamine is also a metabolite of benzphetamine, a schedule C-III prescription medication for treating obesity. These sources of methamphetamine are expected to be virtually 100% *d*-methamphetamine ( $\geq 95\%$ ).

Alternatively, combined use of both a *d*-methamphetamine pharmaceutical product and a *l*-methamphetamine pharmaceutical or OTC product may result in a percentage greater than 5 but less than 95 for the *d*- and *l*-isomers (mixture of isomers). However, given the unlikelihood that a patient is taking two different methamphetamine-containing medications, results where the *d*- or *l*-isomer percentage is mixed are more probably a result of illicit use.

### C. Stereospecific Isomer Testing

Routine definitive testing does not effectively differentiate between *d*- and *l*-forms of methamphetamine. Specialized testing performed on urine and oral fluid

samples, such as stereospecific chromatography, are used to distinguish between isomers. If a patient reports use of an OTC vapoinhaler, a healthcare professional may request the stereospecific test in addition to definitive testing to confirm the reported source. Of note, maximum detected concentrations of methamphetamine in urine and oral fluid after controlled administration of an OTC nasal decongestant inhaler containing levmetamfetamine at manufacturer recommended doses were 1,440 ng/ml and 380 ng/ml, respectively.<sup>12,13</sup> However, concentrations up to 6,000 ng/mL in urine have been reported with suprathreshold doses.<sup>14</sup>

Stereospecific testing should not be requested to rule out use of OTC products such as pseudoephedrine, as these have already been ruled out during definitive testing. For compounds which result in positives for *d*-methamphetamine or *l*-methamphetamine, refer to Table 14.2.

Table 14.2: *D/L Isomer Stereospecific Test*

ISOMER RESULT	POTENTIAL SOURCES
<i>Stimulant form present (d ≥95%, l ≤5%)</i>	<ul style="list-style-type: none"> <li>• Prescription methamphetamine (Desoxyn<sup>®</sup>)</li> <li>• Prescription benzphetamine</li> <li>• Illicit methamphetamine</li> </ul>
<i>Mix of non-stimulant and stimulant forms present (d and l are both &gt;5 but &lt;95)</i>	<ul style="list-style-type: none"> <li>• Illicit methamphetamine</li> <li>• Combination of medications containing <i>d</i>-methamphetamine- and <i>l</i>-methamphetamine-only</li> </ul>
<i>Non-stimulant form present (l ≥95%, d ≤5%)</i>	<ul style="list-style-type: none"> <li>• Selegiline (EMSAM<sup>®</sup>, Zelapar<sup>®</sup>)</li> <li>• OTC vapoinhaler containing levmetamfetamine</li> <li>• Illicit methamphetamine</li> </ul>

#### REFERENCES:

1. Baselt RC. *Disposition of toxic drugs and chemicals in man*. 11th ed. Seal Beach, CA: Biomedical Publications; 2017.
2. Gourlay DL, Heit HA, Caplan YH. *Urine drug testing in clinical practice: the art and science of patient care*. 6th ed. Stamford, CT: PharmaCom Group, Inc.; 2015:1-32.
3. Cody JT. Precursor medications as a source of methamphetamine and or amphetamine positive drug testing results. *J Occup Environ Med*. 2002;44(5):435-50
4. Vidal Gine C, Ventura Vilamala M, Fornis Espinosa I, et al. Crystals and tablets in the Spanish ecstasy market 2000-2014: Are they the same or different in terms of purity and adulteration? *Forensic Sci Int*. 2016;263:164-8.
5. Jemionek JF, Addison J, Past MR. Low concentrations of methamphetamine detectable in urine in the presence of high

- concentrations of amphetamine. *J Anal Toxicol*. 2009;33:170-3.
6. Fleming S, Wolfe L, Meeker J. Expanded evaluation of patients prescribed Adderall® and Vyvanse® for the presence of methamphetamine. Poster presented at: Society of Forensic Toxicologists Annual Meeting; October 2015; Atlanta, GA.
  7. Wang T, Shen B, Shi Y, Xiang P, Yu Z. Chiral separation and determination of R/S-methamphetamine and its metabolite R/S-amphetamine in urine using LC-MS/MS. *Forensic Sci Int*. 2015;246:72-8.
  8. Manley SY, Watson AR. Determining the prevalence of d/l-methamphetamine in urine samples of healthcare patients. Poster presented at: 2018 Tennessee Pharmacists Association Winter Meeting; February 27, 2018; Nashville, TN.
  9. The Drug Enforcement Administration, Office of Forensic Sciences. "ICE" l-methamphetamine HCl on the west coast. *Microgram Bulletin*. 2003;36(11):251.
  10. The Drug Enforcement Administration, Office of Forensic Sciences. Unusual l-methamphetamine clandestine laboratory in Los Angeles, California. *Microgram Bulletin*. 2004;37(6):65-6.
  11. Mendelson J, Uemura N, Jones R, et al. Human pharmacology of the methamphetamine stereoisomers. *Clin Pharm Ther*. 2006;80(4):403-20.
  12. Smith M, Nichols D, Underwood P, et al. Methamphetamine and amphetamine isomer concentrations in human urine following controlled Vicks VapoInhaler administration. *J Anal Toxicol*. 2014;38(8):524-7.
  13. Newmeyer MN, Concheiro M, da Costa J, Flegel R, Gorelick DA, Huestis MA. Oral fluid with three modes of collection and plasma methamphetamine and amphetamine enantiomer concentrations after controlled intranasal l-methamphetamine administration. *Drug Test Anal*. 2015;7(10):877-83.
  14. Fitzgerald R, Ramos J, Bogema S, Poklis A. Resolution of methamphetamine stereoisomers in urine drug testing: urinary excretion of R(-)-methamphetamine following use of nasal inhalers. *J nal Toxicol*. 1988;12(5):255-9.