行政院所屬各機關因公出國人員出國報告書

(出國類別：參加國際會議)

參加「2003年美國第三十四屆鑑識毒物科學家年會」報告

服務機關：行政院衛生署管制藥品管理局

出 國 人　職　　稱：薦任技士

姓　　名：徐　睿

出國地點：美國奧勒岡州波特蘭市

出國期間：自92年10月18日至92年10月27日

報告日期：中華民國92年12月27日

系統識別號:C09204465

公 務 出 國 報 告 提 要

頁數: 17　含附件: 否

報告名稱:

參加2003年美國第三十四屆鑑識毒物科學家年會

主辦機關:

行政院衛生署管制藥品管理局

聯絡人／電話:

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徐睿　行政院衛生署管制藥品管理局　篩檢認證組　薦任技士

出國類別: 其他

出國地區: 美國

出國期間: 民國 92 年 10 月 18 日 -民國 92 年 10 月 27 日

報告日期: 民國 92 年 12 月 27 日

分類號/目: J0／綜合（醫藥類）　J0／綜合（醫藥類）

關鍵詞:　鑑識毒物

內容摘要: 2003年美國第三十四屆鑑識毒物科學家年會，於民國92年10月20日至10月24日在奧勒岡州波特蘭市DoubleTree Hotel Portland-Lloyd Center舉行，來自全美各地、歐洲及亞洲各國之學者專家、毒物檢驗人員共聚一堂，就毒物科學相關議題發表心得報告，年會會議包括專題研討會、科學議程、事務會議、儀器廠商展示等，其中專題研討會、科學議程及事程會議，從早上八時至晚上九時，依不同主題展開討論或研討會。本次年會研討範圍包括鑑識毒物分析、藥物濫用案例分析、藥物濫用對駕駛行爲影響及藥物在毛髮、生體液分析技術探討等，其中專題研討會10場，科學議程論文發表包括口頭論文報告及壁報論文展示，有近百篇論文於會中發展。參加「液相層析質譜儀在例行的鑑識毒物學之實際應用」、「檢體前處理之原理」、「聯邦法規定藥物檢測的發展」等三項專題研討會，以瞭解液相層析質譜儀在目前例行的鑑識毒物學之實際應用情形、樣品前處理之現況及未來發展方向及美國聯邦政府規定藥物檢測之發展方向，並藉由參與科學議程之研討及發表「Abuse of Methylene- dioxymethamphetamine in Taiwan ¾ Analytical Approaches and Analytes Distribution in Antemortem and Postmortem Specimens」壁報論文，汲取新知，互相交換心得、資訊，瞭解濫用藥物相關檢驗技術、發展趨勢，以爲加強濫用藥物防制參考。

本文電子檔已上傳至出國報告資訊網

摘 要

2003 年美國第三十四屆鑑識毒物科學家年會，於民國 92 年 10 月 20 日至 10 月 24 日在奧勒岡州波特蘭市 DoubleTree Hotel Portland-Lloyd Center 舉行，來自全美各地、歐洲及亞洲各國之學者專家、毒物檢驗人員共聚一堂，就毒物科學相關議題發表心得報告，年會會議包括專題研討會、科學議程、事務會議、儀器廠商展示等，其中專題研討會、科學議程及事程會議，從早上八時至晚上九時，依不同主題展開討論或研討會。

本次年會研討範圍包括鑑識毒物分析、藥物濫用案例分析、藥物濫用對駕駛行為影響及藥物在毛髮、生體液分析技術探討等，其中專題研討會 10 場，科學議程論文發表包括口頭論文報告及壁報論文展示，有近百篇論文於會中發展。

參加「液相層析質譜儀在例行的鑑識毒物學之實際應用」、「檢體前處理之原理」、「聯邦法規定藥物檢測的發展」等三項專題研討會，以瞭解液相層析質譜儀在目前例行的鑑識毒物學之實際應用情形、樣品前處理之現況及未來發展方向及美國聯邦政府規定藥物檢測之發展方向，並藉由參與科學議程之研討及發表「Abuse of Methylene-dioxymethamphetamine in Taiwan — Analytical Approaches and Analytes Distribution in Antemortem and Postmortem Specimens」壁報論文，汲取新知，互相交換心得、資訊，瞭解濫用藥物相關檢驗技術、發展趨勢，以為加強濫用藥物防制參考。

參加「2003 年美國第三十四屆鑑識毒物科學家年會」報告

目　錄

第一章　目　的

2003 年美國第三十四屆鑑識毒物科學家年會（SOFT，Society of Forensic Toxicologists），於民國 92 年 10 月 20 日至 24 日，在奧勒岡州波特蘭市 DoubleTree Hotel-Lloyd Center 舉行，研討範圍包括鑑識毒物分析、藥物濫用案例分析、藥物濫用對駕駛行為影響及藥物在毛髮、生體液分析技術探討等。行政院衛生署管制藥品管理局篩檢認證組負責篩檢認證管理方案之規劃、研擬、評估及辦理濫用藥物檢測業務，因應國際化趨勢亟提升業務職能；為有效防制藥物濫用，亟需監測新興藥物種類，建立分析新興藥物技術，瞭解藥物濫用變化趨勢；同時面對檢測技術逐漸提升之國際化潮流，瞭解濫用藥物科技新知及其檢測技術，藉由出席此次會議，以瞭解美國鑑識毒物之分析及應用情形，建立國際交流管道。

第二章　過　程

10 月 18 日　自中正國際機場搭乘長榮航空班機經西雅圖轉全美航空班機，前往美國奧勒岡州波特蘭市

10 月 19 日　抵達波特蘭市，赴大會會場辦理報到手續。

10 月 20 日　專題研討會

1. Practical Applications of LC/MS in Routine Forensic Toxicology
2. Principles of Sample Preparation

10 月 21 日　專題研討會：Developments in Federally Regulated Drug
儀器書籍攤位展示、大會歡迎晚會

10 月 22 日　大會演講
主題：Opiate Update: From Obesity to Dependency
科學論文發表、儀器書籍攤位展示

10 月 23 日　大會演講
主題：Mechanisms Underlying Tolerance to Methamphetamine
科學論文發表、壁報論文展示、儀器書籍攤位展示、SOFT President's Reception
壁報論文展示
Abuse of Methylenedioxymethamphetamine in Taiwan — Analytical Approaches and Analytes Distribution in Antemortem and Postmortem Specimens

10 月 24 日　大會演講
主題：A Serial Arsenic and Thallium Poisoning in a Small Midwestern Town
科學論文發表、壁報論文展示、離別餐會

10 月 26 日　搭乘聯合航空班機自奧勒岡州波特蘭國際機場至洛杉磯國際機場轉長榮航空班機

10 月 27 日　抵達中正國際機場

第三章　心　得

SOFT 年會特色之一為與 Journal of Analytical Toxicology（JAT）合作，在 JAT 每年的定期刊物中均會有一期專門刊載相關鑑識毒物的研究論文，並在 SOFT 年會上發給每一位與會人員此一期刊，且在 SOFT 年會上所發表的論文摘要也會以特別報導的方式適時地刊載於 JAT 期刊上。今年 JAT 最新一期的十月份期刊即完全刊載鑑識毒物相關的研究論文，本局適逢在李局長志恒及科技諮詢專家劉教授瑞厚的指導下也有一篇研究論文「Performance Characteristics of Latest Immunoassays for Preliminary Test of MDMA and Related Drugs in Urine Specimens」發表於其上。

年會中參加「液相層析質譜儀在例行的鑑識毒物學之實際應用」、「檢體前處理之原理」、「聯邦法規定藥物檢測的發展」等三項專題研討課程，科學論文報告、壁報論文展示活動。本局今年與法務部法醫研究所合作，有一篇壁報論文「Abuse of Methylene-dioxymethamphetamine in Taiwan — Analytical Approaches and Analytes Distribution in Antemortem and Postmortem Specimens」參展。以下就相關課程、議程，提出最新重要資訊及心得報告。

一、 專題研討會

（一）液相層析質譜儀在例行的鑑識毒物學之實際應用

氣相層析質譜儀（GC/MS，Gas Chromatography/Mass Spectrum）不宜用來分析分子量較大、熱不穩定或極性較大等樣品，液相層析質譜儀（LC/MS，Liquid Chromatography/Mass Spectrum）可彌補此一遺憾。本單元涵蓋液相層析質譜儀之種類、方法、靈敏度、精確度、應用範圍、案例分析及經驗分享交流。在鑑識毒物實驗室，液

相層析儀與不同種類之質譜儀如單一四極棒（Singal Quad）、離子阱（Ion Trap）、三段四極棒（Triple Quad）和飛行式（TOF，Time of Flight）等相結合成一非常有用之分析工具。除了講解液相層析質譜儀之原理、理論基礎、分析步驟、數據資料之應用及解讀外，並以案例分析來闡明液相層析質譜儀在鑑識毒物分析之實際應用。會中並於現場討論部分，藉由同一種藥品（分析物）分別以液相層析質譜儀與氣相層析質譜儀分析後之結果，比較其各自之優、缺點。講者並建議儀器分析使用者永遠採用 MS/MS 分析模式以獲得較多的資訊。

液相層析質譜儀應用於鑑識毒物分析上，其優點有可省略衍生化步驟、增進偵測極限及縮短萃取/分析時間。LC/MS/MS 適用於不用的樣品前處理方法，目前 LC/MS/MS 分析方法運用在鑑識毒物例行性檢測上的有 Benzodiazepines、Blood THC and 9-Carboxy-THC、Paroxetine、Propoxyphene 等，正在發展中的則有安非他命、Trazodone、Verapamil、Morphine glucuronides 等。

（二）檢體前處理之原理

本單元針對目前鑑識毒物實驗室應用之檢體前處理方法如水解（Hydrolysis）、液/液相萃取法（Liquid/liquid phase extraction）、固相萃取法（Solid phase extraction）及固相微小萃取法（Solid phase micro-extraction）等方法就其原理、理論基礎、分析步驟、應用範圍及其優缺點等加以闡述並舉例說明。除了闡明固態微小萃取法在鑑識毒物分析上之限制如檢體黏稠性影響萃取效率等外，並陳述鑑識毒物分析之檢體前處理方法上，頂空萃取法（Headspace extraction）屬於較新之技術，其除適用於酒精等揮發性藥物分析外尚適用於安非他命及甲基安非他命等半揮發性藥物檢測。會中除比較毛髮、生體液（如唾液、汗液等）等檢體與尿液檢體在採集及檢

體前處理方法上的優缺點，並提供了毛髮、生體液等檢體之採集方法、檢體前處理方法、物質濫用暨精神衛生防治局（SAMHSA，Substance Abuse and Mental Health Services Administration）所訂之閾值參考值及其相關之文獻。

1、水解

水解方法有酸水解、鹼水解及酵素水解三種。酸水解方法用於鴉片、Benzodiazepines 等，鹼水解方法有效於酯鏈結的 glucuronide 結合物如大麻尿液中主要代謝物等，二者之優點為快速、便宜和完全，缺點為不具選擇性、強酸/鹼易分解檢體/分析物，酵素水解方法最常見為β-glucuronidase 和 arylsulfatase 這兩種酵素，glucuronidase 對醚和酯鏈結之結合物均有效，其優點為沒有檢體/分析物被分解、具選擇性，缺點為較昂貴、需較長時間。

2、萃取法

萃取方法有液/液相萃取、固相萃取、固相微小萃取及頂空萃取等方法，如何選擇一適當的萃取方法則視分析物特性、經費、人力、時間等各因素決定。固相萃取法通常較快速、容易自動化但其較為昂貴、需較多經費，液/液相萃取法之方法大多已建立但缺乏固相萃取法之變通性、乳化通常為其問題、需用到較多溶劑。

3、尿液替代物

考慮毛髮、生體液（如唾液、汗液等）等檢體為尿液替代物之好處為較長偵測期（wider window of detection）：毛髮為 90 天、尿液及唾液為 2-3 天、汗液為數天，一般較長之偵測期者其相對應之閾值較低；毛髮可提供定量及歷史資料；無等待收集時間；摻假機會低、不需隱密採尿室、不需冰箱、容易處理及運送、無生物危害性等。缺點為毛髮易受染劑、環境污染物等干擾，清洗步驟較為繁複。

（三）聯邦政府規定藥物檢測的發展

本單元著重在聯邦工作場所藥物檢測計畫的討論。物質濫用暨精神衛生防治局（SAMHSA）工作人員將針對目前工作場所藥物檢測的議題、替代介質（如毛髮、唾液、汗液等）的檢測、收集場所程序和經由藥物綜評醫師（MRO，Medical Review Officer）評估結果報告的品質保證計畫等來討論工作場所尿液檢測的不實性、結果和關心重點。

1、推翻工作場所藥物檢測之方法

如何獲得一有效的檢體是一個一直廣受爭論的議題，雖在監視檢體收集方面可將干涉降至最低，但僅用於在合理的懷疑或特別再收集的情況下，而在非監視、例行性檢體收集方面仍是有機會藉稀釋、調換、摻假或清潔產品的使用等方法來推翻工作場所藥物檢測。會中詳細介紹稀釋劑、摻假物、清潔產品及尿液代替物這四種產品的成分及價格，並論及這些產品可由雜誌、減肥藥零售商、煙草商及網路等管道輕易取得。雖然有要求檢體須做有效性測試但其成效是有限的，因摻假物時時在變，特別是當其被認出和反對時。以亞硝酸鹽和鉻酸鹽為例，當亞硝酸鹽被認出及建立閾值濃度及制定檢測方法時，製造商隨即降低亞硝酸鹽濃度至閾值之下，而有些則改用鉻酸鹽。而當鉻酸鹽被認出及有其檢測方法時，製造商又隨即改用亞硝酸鹽/鉻酸鹽之混合物甚至使用新的氧化物（如氫氟酸、過碘酸鹽和其他鹵化族等）。

2、物質濫用暨精神衛生防治局之聯邦工作場所人員強制性藥物檢驗計畫規範修正草案

工作場所藥物檢測計畫於 1988 年建立，藥物檢測之範圍包括受聘僱前、隨機、意外事件後、合理的懷疑/原因、回到原工作、後續追蹤及其他（如自願等），對象有聯邦政府官員、交通運輸部及核能

法規委員會規定的企業等，其檢測受檢者尿液檢體中濫用藥物的含量是否有超過法定閾值。尿液檢體的好處為檢測方法已建立且運作良好，缺點為具侵入性、易被調包、摻假、運送時易發生外漏及分析物分解等。

目前之聯邦工作場所人員強制性藥物檢驗計畫規範為 1994 年起生效，物質濫用暨精神衛生防治局於 1997 年 4 月提出藥物檢驗計畫規範修正草案第一版而現在最新版草案為2001年9月所提出的第四版，最新版之草案內容與目前使用之版本不同處有選擇代替之生物檢體（如毛髮、生體液等）及其藥物檢測技術和執行藥物檢測之場所。替代檢體的好處有侵入性小、可多次取樣、檢體穩定性高、容易運送及貯存、不易被替代及摻假。缺點為需處理較低分析物濃度、需較敏感分析方法如 GC/MS/MS 等、需檢測原型藥而非其代謝物或者兩者均需檢測等。一般考量的需求性層面有科學、法庭/法規及社區的可接受性、食品藥物管理局（FDA，Food and Drug Administration）同意、閾值的建立、成本效益等、最重要的是每一檢測結果必須是正確的及可信賴的。

在執行藥物檢測之場所方面有現場採驗（POCT，Point of Collection Test）和初篩儀器檢驗機構（IITF，Instrumented Initial Test Facility），現場採驗為在採樣現場執行的初步檢驗以決定檢體是否含藥物及/或呈現檢體之真實性，可現場採驗之檢體有尿液和唾液。認可之初篩儀器檢驗機構是指在一個固定的地點具備執行藥物之初步檢驗儀器測定和檢體真實性檢驗的能力之機構，初篩儀器檢驗機構可檢驗毛髮、尿液、汗液和唾液。兩者之潛在優點為對非-陰性檢體有較快之 turn around time、較快之人為決定和成本效益，潛在缺點為測試人員之訓練、績效維持、格外的檢體監管紀錄文件。

此修正草案已經美國衛生福利部（DHHS，Department of Health and Human Services）通過，近期內將公告於聯邦政府公報（Federal Register）請大眾提供意見。

3、檢體檢測結果之統計資料分析

根據聯邦工作場所人員強制性藥物檢驗計畫規範，經政府衛生福利部認可之藥物檢測分析實驗室須定期提供檢體檢測之統計相關資料給執行機關。藥物檢測指標（Drug Test Index）資料庫始於 1988 年，最初統計指標為整體之檢出陽性率，於 1991、1992 年統計指標除整體之檢出陽性率外，尚有從事與安全有關之聯邦政府僱員強制性檢測（FMSS，Federally-Mandated Safety Sensitive）與一般民間工作場所（GW，General Workplace）之檢出陽性率，於 1997 年統計指標多了以藥物分類和以地區別後三碼之檢出陽性率，並於 1999 年加入檢體有效性檢測（specimen validity test）之統計資料。統計分析各認可實驗室所提供的數據結果，FMSS 的整體檢出陽性率自 1998 年起持續下降，GW 受聘僱員工之整體檢出陽性率約為聯邦僱員的 1.5-2 倍，且安非他命檢測陽性率自 1998 年起逐年小幅度增加。

二、大會議程

大會特別邀請到總統辦公室有關國家藥物控制政策之藥物損害駕駛委員會（Drug Impaired Driving Committee）的 Mr. John Horton 前來演講，題目為「National Policy Initiatives on Drugs and Driving」，其闡述因駕駛者使用藥物而影響交通安全問題日益嚴重，聯邦政府努力致力於防範駕駛者藥物濫用以保障大眾安全。大會並針對藥物濫用對駕駛行為影響作一專題研討。美國華盛頓州的鑑識毒物實驗室特別針對因藥物濫用對駕駛危害性影響作一系列研究，資料顯示在交通致死案件分析資料中顯示藥物及酒精的使用仍為主要發現之一，但近十

年來因使用酒精所造成的致死案件有逐漸減少，而一些藥物如甲基安非他命等之使用所造成的致死案件則顯著增加。天使塵、Lorazepam、麻黃素等藥物均會影響駕駛能力；Lorazepam 為 Benzodiazepine 的一種用來治療失眠、憂鬱，一般常見的副作用包括虛弱、精神不濟、昏眩和失去方向感等，在分析 128 件呈 Lorazepam 藥物反應交通事故案件，資料結果駕駛者的心理性肌肉協調能力下降，走路、旋轉及單腳站立測試表現不良，顯示了 Lorazepam 足以顯著影響駕駛安全性。在麻黃素的案件分析中，案主連續二次因異於常軌之駕駛行為被逮捕，其平衡不良、行為舉止異常誇大、多話、走路、旋轉及單腳站立測試表現不良，經調查為案主持續服用過量之麻黃素以保持精神狀態清醒。

維吉尼亞大學醫學院病理所 Carl Wolf 先生則針對維吉尼亞州 Commonwealth 地區於 2001 年 7 月至 2002 年 12 月間 2948 件因藥物濫用影響駕駛行為案件進行分析，檢測血中十餘種藥物及其濃度，結果發現案件中藥物檢出件數仍以酒精居第一位，大麻次之，Alprazolam、Nordiazepam 等 Benzodiazepine 藥物分居三、四位。

三、科學議程

本議程分口頭論文發表及壁報論文展示，以下就業務相關論文提出心得報告。

在快速簡易篩檢試劑評估方面，田那西州的 Howard Taylor 先生對 DrugCheck®9 On-Site Immunoassay Test Cup 進行評估，DrugCheck®9 On-Site Immunoassay Test Cup 為一種一次可以同時分析九種分析物（如安非他命、甲基安非他命、大麻、古柯鹼代謝物、天使塵、鴉片類、Benzodiazepine、巴比妥類及 TCA 等）的直讀式、定性免疫學分析檢驗杯。其研究依據免疫學分析有效性之 NLCP 規範

進行，136 個檢體除以 DrugCheck®9 On-Site Immunoassay Test Cup 分析外並同時用 CEDIA 免疫學試劑及 GC/MS 進行分析，數據比對結果，test cup 檢出陽性、陰性與 CEDIA 和 GC/MS 檢出結果符合程度高達 97.8% 。羅氏藥廠的 K. Hon 先生評估 Roche ONLINE DAT II Methadone, Cocaine and Cannabinoid Assays 之成效，50 個檢體除以 ONLINE DAT II 分析外並同時以 CEDIA DAU Cocaine 免疫學試劑、HPLC REMEDi Screen 及 LC/MS 進行比對，結果顯示 ONLINE DAT II 除了有好的正確率、回收率及檢量線穩定外，檢出結果經與其他免疫學試劑及確認方法比對亦有良好符合程度。

在摻假檢測評估方面，美國猶他州鹽湖城的西北毒物學公司（Northwest Toxicology Inc.）對摻假藥物尿液檢體檢測作一系列研究。Kris Botelho 先生對 Axiom Diagnostics 的 Test True Oxidant Assay、Dade Behring 的 Ox Perfect Test、 Kasey Inc. 的 Lark Oxidant Reagen 和 Norwest Toxicology Inc.（NWT）的 Oxidant Reagent 四種氧化試劑是否能確認出經添加氧化劑和其他足以干擾分析物質之尿液檢體的有效性進行比較評估，其用漂白劑、三價鉻、六價鉻、肥皂、Urine Luck 6.0，6.5、Klear Double Shot、Oxone、5% 及 25% 血和 Silver Nitrate 等二十五種溶液添加於尿液檢體中，以 Hitachi 747 自動生化分析儀分析，結果顯示以整體而言 Axiom Diagnostics 的試劑表現最好，NWT 試劑次之。Chuck Jones 先生利用 HPLC 方法檢測摻有六價鉻的尿液檢體中六價鉻的含量及評估其經冷凍貯存後之穩定性，尿液檢體先經 1,5-diphenylcarbazide 處理，strychnine 為內標準品，以 HPLC-UV 檢測波長 540nm 的六價鉻。含六價鉻的尿液檢體經冷凍貯存後，其數值明顯變動，尿液檢體經冷凍二至十八個月後，其檢測值平均減少 18.9%，但陽性檢體仍可預期其再檢測值可高於 LOQ。此 HPLC 方法用以檢測和定量六價鉻是快速且有效。Charles Jones 先生

評估冷凍貯存對摻有亞硝酸鹽之尿液檢體的影響，檢測方法以氧化試劑/自動生化分析儀為初步篩檢方法，nitrite specific dipstick、Ion Chromatography （IC）、Atomic Absorption（AA）和 Capillary Electrophoresis（CE）為確認檢測方法。冷凍貯存對尿液檢體確實有影響，尿液檢體經冷凍二至十二個月後，其檢測值平均減少 20%，但它不能干擾摻有亞硝酸鹽之尿液檢體在 LOQ 濃度範圍的再確認檢測值。路易斯安那州的 Barbara Manno 女士分析評估草藥製品的使用對鑑識尿液濫用藥物檢測之影響。

在毛髮檢測方面，猶他大學人體毒物學中心的 Day 先生利用 LC/MS 分析毛髮中五種鴉片主要生物鹼的含量，此方法用於分析 34 疑似使用鴉片者的真實人體毛髮檢體，在這些檢體中，七個被檢出二種或二種以上化合物呈陽性反應。沒有毛髮檢體檢出含有 6-MAM。內華達州的 Craig Setter 先生對 OraSure、Immunalysis、Neogen 和 International Diagnostic Systems 四種商業化用以分析 THC-COOH 的 ELISA 套組（Kits）進行毛髮檢體分析之有效性的比較評估，結果顯示 OraSure、Immunalysis 和 International Diagnostic Systems 三種 ELISA 套組可達毛髮檢體分析所需之檢測標準。Immunalysis 和 International Diagnostic Systems 此二種 ELISA 套組可進一步達到 1pg/mg 的篩檢閾值。

本局於會中發表之壁報論文「Abuse of Methylenedioxymethamphetamine in Taiwan — Analytical Approaches and Analytes Distribution in Antemortem and Postmortem Specimens」，本論文係今年科技諮詢專家劉瑞厚教授在法務部法醫研究所指導 MDMA 研究時，指導彙整分析 2001 年 6 月至 2003 年 7 月間收集之 20 組死後檢體包括心臟血液、腸內容物、尿液和膽汁等檢體、25 個臨死前尿液檢體及 6 個臨死前毛髮檢體之檢出 MDMA 情形，論文內容詳如附件一。本論文吸引許

多志同道合與會人士觀看，並提出相關問題，相互交換意見，特別是美國一些實驗室在做 MDMA 死後檢體及臨死前尿液檢體分析時會一併檢測 Caffeine 含量。

第四章　建　議

一、建立濫用藥物尿液檢體替代物方案，符合國內需求、因應國際潮流趨勢

目前國內濫用藥物之檢測是檢驗毒品使用嫌疑犯之尿液檢體中濫用藥物含量是否超過法定閾值，考量尿液檢體取得不易、易受人體代謝速率影響、採集時間限制及毛髮、生體液之檢體穩定性高、容易運送及貯存、不易被替代及摻假且其分析檢驗技術已日漸純熟等因素，美國物質濫用暨精神衛生防治局近年來集思除了尿液外，是否有其他適合用以檢測濫用藥物含量之生物檢體即是否有尿液檢體替代物。本署一些濫用藥物尿液認可檢驗機構近年來也努力開發除現有之濫用藥物尿液檢驗方法外之濫用藥物生物檢體（如毛髮、生體液等）檢驗方法以配合民眾（尤其是父母）需求。故選擇及建立一適當之濫用藥物尿液檢體替代物已是國內、外濫用藥物檢測之產、官、學等各界所亟需努力思考方向。

二、持續加強建立濫用藥物檢測技術、相關資訊擷取之管道

藥用濫用問題是無國界之分，已為全球性之議題。國際間濫用藥物檢測技術如 GC/MS/MS、LC/MS/MS、固相微小萃取法（SPME）、頂空萃取法（Headspace extraction）、毛細管電泳分析等應用發展，毛髮、生體液等分析方法之開發，可參考國外技術引進，再加以調整，使局內檢驗科技研究更有效率，有助提升國內檢驗技術水準。

三、加強藥物濫用對駕駛行為影響之相關研究

因藥物濫用所造成的交通事故與日俱增，美國華盛頓州及維吉尼亞州分別針對其境內之藥物濫用對駕駛行為影響的案件作一系列研究分析，結果顯示近十年來因使用酒精所造成的致死案件有逐漸減

少，但一些藥物如甲基安非他命等之使用所造成的致死案件和因服用安眠鎮靜劑造成之交通事故案件則有顯著增加。目前國內雖有針對駕駛人員作酒精濃度測試的道路臨檢工作，卻無對其是否因吸食濫用藥品所造成之行為舉止反應異常作觀察、檢測。而國內針對藥物濫用對駕駛行為影響之相關研究報導也不多見，實有加強之必要性。

附件一

Abuse of Methylenedioxymethamphetamine (MDMA) in Taiwan — Analytical Approaches and Analytes Distribution in Antemortem and Postmortem Specimens

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ABSTRACT

With increasing requests for the analysis of various specimens related to fatal and non-fatal abuse of methylenedioxy-methamphetamine (ecstasy, MDMA), the toxicology laboratory of the Institute of Forensic Medicine has established appropriate protocols for the analysis of MDMA and related compounds in hair, urine, and various postmortem specimens.

Analytical protocols include extraction, derivatization, and GC-MS analysis adapting deuterated analogs of the analytes as internal standards. Data resulting from these analyses and hereby reported include (a) postmortem distribution of MDMA and MDA in heart blood, gastric content, urine, and bile specimens from 20 fatal cases; (b) other drugs found in the heart blood from these 20 cases; and (c) the distributions of MDMA and MDA in 25 antemortem urine and six hair specimens. Data summarized in Table 1 are compared to those reported in the literature [1–7] and discussed.

The MDA/MDMA concentration ratio observed in a limited number of hair specimens ($n = 6$) are consistent and *appear* to be higher than those found in other specimens. Compared to other commonly abused drugs, e.g., cocaine and heroin, the "metabolite/parent drug" concentration ratio (MDA/MDMA) in hair is not significantly different from the ratios derived from other specimens, such as urine and blood. This observation is consistent with the relative drug/metabolite incorporation rates reported for cocaine/benzoylecgonine, tetrahydrocannabinol/tetrahydrocannabinoic acid, and MDMA/MDA [8].

Table 1. The highest MDMA levels[a] and the ranges of MDA/MDMA ratio found in ante- and postmortem specimens analyzed in our laboratory

Specimen	Highest MDMA concentration	MDA/MDMA ratio observed: Range	Mean	Std dev	Mean ± 2 std dev	Literature reference
Urine ($n = 10$)	67.115	<0.011–0.174	0.061	0.049	0.038–0.160	[1]
Bile ($n = 8$)	130.952	<0.011–0.146	0.057	0.045	0.000–0.147	[1]
Gastric ($n = 12$)	40.515	<0.004–0.463	0.086	0.130	0.000–0.346	[2]
Heart blood ($n = 15$)	40.412	<0.014–0.045	0.069	0.053	0.000–0.174	[3,4]
Hair ($n = 6$)[b]	59.91	0.128–0.211	0.160	0.032	0.096–0.224	[5,6]
Urine ($n = 22$)[b]	33.31	0.014–0.236	0.101	0.052	0.000–0.205	[7]

[a] In ng/mg for hair; in μg/mL for other specimens.

[b] Antemortem specimens.

INTRODUCTION / BACKGROUND

- Taiwan has, in recent years, experienced a very significant increase in the abuse of methylenedioxymethamphetamine (ecstasy, MDMA) [9].
- Requests for the analysis of post- and antemortem specimens related to fatal and non-fatal abuse of MDMA received by the Institute of Forensic Medicine have also significantly increased.
- Protocols for the analysis of MDMA and related compounds in hair, urine, and various postmortem specimens have been established and hereby reported.
- Analytical data hereby reported include:
    - Postmortem distribution of MDMA and MDA in heart blood, gastric content, urine, and bile from 20 MDMA-induced (or related) fatal cases;
    - The distribution of MDMA and MDA in 25 antemortem urine and 6 hair specimens; and
    - Other drugs found in the heart blood from the 20 fatal cases.

EXPERIMENTAL DESIGN

Samples

- Twenty sets of postmortem specimens received during the period of June 2001 to July 2003. Most of these sets include heart blood, gastric content, urine, and bile specimens, while one or two specimens (typically bile or urine) are missing in some of these sets.
- Twenty-five antemortem urine specimens.
- Six antemortem hair specimens.

Sample Pretreatment — Extraction and Derivatization (Figure 1)

- Liquid-liquid extraction was adapted as the basis for sample pretreatment.
- Hair specimens were processed differently from other specimens, such as urine, gastric, and blood (*see* the upper portion of Figure 1).
- Heptafluorobutyl (HFB)-derivatives of the analytes and the internal standards were found to generate the most favorable mass spectrametric data for GC-MS analysis and adapted for the analysis of all specimens [10].
- Derivatization was carrid out by dissolving the extraction residue in ethyl acetate, followed by reacting with heptafluorobutyric anhydride at 70 °C for 20 minutes (*see* the lower portion of Figure 1).

GC-MS Analysis

- Instrumentation: Agilent 6890 GC/5972N MSD with HP-1MS (30-m, 0.25-mm ID, 0.25-μm film thickness).
- Column temperature: From 60 °C (1 min) to 300 °C (1 min) at 20 °C/min; Injector: 260 °C; Interface: 280 °C.
- Full-scan mass spectra of the analytes and the internal standards are shown in **Figure 2**.
- Quantitation
    - Internal standards: MDMA-d_5 and MDA-d_5 (*see* Figure 2 for their structures); ions designated for MDMA, MDMA-d_5, MDA, and MDA-d_5 are *m/z* 254, 258, 162, and 167, respectively.
    - Calibrations: Five-point calibrators at 100, 250, 500, 1000, and 2000 ng/mL for urine, gastric, blood, and bile; and at 2, 5, 10, 20, and 40 ng/mg for hair specimens.

RESULTS and DISCUSSION

Distribution of MDMA and MDA in Postmortem and Antemortem Specimens

- Postmortem Specimens — Heart blood, Gastric, Urine, Bile
    - Distribution of MDMA and MDA in heart blood, gastric, urine, and bile specimens from 20 MDMA-induced (or related) fatal cases (June 2001 to July 2003) tested in this laboratory are listed in **Table 2**.
    - With no MDMA detected, Cases 10 and 13 are most likely caused by the ingestion of MDA.
    - Some statistical data of the findings from these 20 cases are listed in **Table 1** (in the **Abstract** section) and summarized as follows:
        - Gastric contains significant amounts of the drug (MDMA or MDA).
        - The wide range of MDA/MDMA ratios found in gastric samples may reflect variations in the duration between drug intake and the time of death.
        - The MDA/MDMA ratios observed in urine, bile, and heart blood specimens are not significantly different.

- Antemortem Specimens — Hair
  - Distribution of MDMA and MDA in antemortem hair samples collected from 6 individuals are shown in **Table 3.**
  - Some statistical data are summarized in **Table 1** (in the **Abstract** section).
  - MDA/MDMA ratios derived from this limited number of specimens (n = 6) are consistent and *appear* to be higher than the corresponding ratios derived from other biological matrices. This is not consistent with an animal (rats) study [6,8] in which MDMA's incorporation rate into hair was found higher than MDA.
- Antemortem Specimens — Urine
  - Distribution of MDMA and MDA in 25 antemortem urine case samples are shown in **Table 4.**
  - Statistical data are summarized in **Table 1** (in the **Abstract** section). Data derived from Cases 15, 20, and 21 are not included in calculating the statistical information shown in Table 1. It is likely that both MDA and MDMA were ingested in Cases 15 and 21.
  - MDA/MDMA ratios shown in Table 4 and summarized in Table 1 are comparable with what have been reported in the literature [1–7].

Characteristics of "Metabolite/Parent Drug" Concentration Ratios in Various Biological Matrices

- MDA/MDMA Ratios Observed among Various Biological Matrices
  - MDA/MDMA ratios derived from a limited number (n = 6) of hair specimens are consistent and *appear* to be higher than those derived from other biological matrices (*see* Table 1).
  - Animal studies (rats) have reported that MDMA's incorporation rate into hair was higher than MDA (2.3 times higher in one study [6] or 0.6 vs. 0.5 in another study by the same group [11]). If this is also true in human, one would expect to see a lower MDA/MDMA ratio in hair than the ratios derived from other biological matrices.
- Comparison of MDA/MDMA Ratio to "Metabolite/Parent Drug" Concentration Ratios Observed for Other Drug Categories, Such as Cocaine, Heroin, and Methamphetamine
  - Animal studies (rats) have reported much higher incorporation rates of cocaine over benzoylecgonine (3.6 vs. 0.003) and 6-acetylmorphine over morphine (0.21 vs. 0.03) [8]; thus, benzoylecgonine/cocaine and morphine/6-acetylmorphine ratios in hair are expected to be much lower than the corresponding ratios derived from other biological matrices. These predictions have been proven true by actual observations.
  - Since the difference between the incorporation rates of MDA and MDMA into hair is much less, the difference in the MDA/MDMA ratios between hair and other biological matrices is expected to be less significant. This is consistent with the observation hereby reported.

CONCLUSION / SUMMARY

- The highest MDMA concentrations observed in 25 antemortem urine and 6 antemortem hair specimens are 33.31 μg/mL and 59.91 ng/mg, respectively.
- The highest MDMA concentrations observed in postmortem heart blood, gastric, bile, and urine specimens derived from 20 MDMA-induced (or related) fatal cases are 40.41, 40.52, 130.95, and 67.12 μg/mL, respectively.
- MDA/MDMA ratios observed in hair *appear* to be slightly higher than the ratios derived from other biological specimens.
- The difference between the MDA/MDMA ratios in hair and other biological matrices is much less significant than the "metabolite/parent drug" ratio differences observed for drug categories such as cocaine, heroin, and marijuana.

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ACKNOWLEDGMENTS

The authors are grateful to the supports provided by the Institute of Forensic Medicine (Taipei, Taiwan) to conduct this study and to Ms. I-Ching Fang for her skillful assistance in compiling the data presented as Tables 1–4.

Table 2. Distributions of MDA and MDMA (μg/mL) in 20 postmortem case specimens

Case	Age	Sex	Drug	Heart blood	Gastric	Urine	Bile	Other drugs (found in heart blood)
1	36	M	MDA	ND[a]	ND	0.588	—[a]	Ethanol
			MDMA	3.045	14.153	28.948	—	
			MDA/MDMA	NA[a]	NA	0.0203	NA	
2	21	M	MDA	0.026	0.311	0.169	ND	ND
			MDMA	1.815	7.047	15.390	6.090	
			MDA/MDMA	0.0143	0.0441	0.0110	NA	
3	23	M	MDA	0.017	0.013	—	—	ND
			MDMA	1.036	0.993	28.948	—	
			MDA/MDMA	0.0164	0.0131	NA	NA	
4	30	F	MDA	0.217	0.873	5.187	—	Codeine, morphine, flurazepam
			MDMA	2.247	10.197	67.115	—	
			MDA/MDMA	0.0966	0.0856	0.0773	NA	
5	20	F	MDA	0.191	0.642	0.292	—	ND
			MDMA	2.539	5.543	4.102	—	
			MDA/MDMA	0.0752	0.1158	0.0712	NA	
6	—	M	MDA	0.034	—	1.398	—	Amphetamine, methamphetamine,
			MDMA	0.231	—	16.993	—	diazepam, nordiazepam, oxazepam,
			MDA/MDMA	0.1472	NA	0.0823	NA	temazepam, ketamine
7	19	M	MDA	0.112	0.242	0.199	0.378	Ketamine
			MDMA	1.630	24.725	6.075	16.021	
			MDA/MDMA	0.0687	0.0098	0.0328	0.0236	
8	20	F	MDA	0.063	0.345	0.677	—	Diazepam, nordiazepam, 7-amino-
			MDMA	0.308	0.745	3.902	—	flurnitrazepam, ketamine
			MDA/MDMA	0.2045	0.4631	0.1735	NA	
9	—	M	MDA	0.301	0.728	2.462	—	ND
			MDMA	4.971	40.515	58.003	—	
			MDA/MDMA	0.0606	0.0180	0.0424	NA	
10	—	—	MDA	5.540	32.869	—	—	Lidocaine
			MDMA	ND	ND	—	—	
			MDA/MDMA	NA	NA	NA	NA	
11[b]	—	F	MDA	2.350	3.714	15.445	—	Diazepam, ketamine, zolpidem
			MDMA	2.449	3.953	16.555	—	
			MDA/MDMA	0.9596	0.9395	0.9330	NA	
12	20	F	MDA	0.070	0.157	0.124	0.161	Codeine, morphine, diazepam,
			MDMA	2.393	37.202	11.340	14.295	nordiazepam, ketamine, lidocaine
			MDA/MDMA	0.0293	0.0042	0.0109	0.0113	
13	20	M	MDA	10.083	28.578	148.847	36.447	ND
			MDMA	ND	ND	ND	ND	
			MDA/MDMA	NA	NA	NA	NA	
14	—	M	MDA	0.094	ND	0.204	0.196	ND
			MDMA	1.011	0.274	2.347	3.094	
			MDA/MDMA	0.0930	NA	0.0869	0.0633	
15	25	M	MDA	0.072	0.254	—	0.323	Diazepam
			MDMA	3.121	19.017	—	7.888	
			MDA/MDMA	0.1430	0.8805	NA	0.1656	

16[b]	25	M	MDA	0.186	0.457	3.614	0.209	Ethanol
			MDMA	1.301	0.519	5.568	1.262	
			MDA/MDMA	0.1430	0.8805	0.6491	0.1656	
17	—	M	MDA	0.285	0.394	—	0.712	Ethanol, atropine, hyoscyamine
			MDMA	3.209	4.024	—	4.792	
			MDA/MDMA	0.0888	0.0979	NA	0.1486	
18	—	M	MDA	0.138	0.500	—	0.207	ND
			MDMA	3.436	3.052	—	2.184	
			MDA/MDMA	0.0402	0.1638	NA	0.0948	
19	25	F	MDA	1.809	5.270	—	5.522	Ketamine
			MDMA	40.412	737.848	—	130.952	
			MDA/MDMA	0.0448	0.0071	NA	0.0422	
20	17	F	MDA	0.115	ND	—	0.218	ND
			MDMA	3.548	32.648	—	6.865	
			MDA/MDMA	0.0324	NA	NA	0.0318	

[a] ND: Not detected (detection limits for urine: MDA, 0.0025 μg/mL; MDMA: 0.001 μg/mL); NA: Not applicable; —: Sample (or information) not available.

[b] Data derived from these 2 case were excluded from the calculation of statistical information shwon in Table 1. Most likely, both MDA and MDMA were digested in Case 11, while some of the data observed derived from Case 16 are not consistent with others..

Table 3. Distributions of MDA and MDMA (ng/mg) in hair from six case specimens

Case	Sex	MDA	MDMA	MDA/MDMA
1	M	3.57	27.86	0.1281
2	F	10.27	59.91	0.1714
3	M	7.71	59.35	0.1299
4	M	6.07	43.11	0.1408
5	F	5.60	31.82	0.1760
6	M	2.96	14.02	0.2111

Table 4. Distributions of MDA and MDMA (μg/mL) in antemortem urine from 25 case specimens

Case	MDA	MDMA	MDA/MDMA
1	0.289	2.325	0.1243
2	0.947	7.015	0.1350
3	0.427	4.323	0.0988
4	0.080	1.915	0.0418
5	0.368	5.444	0.0676
6	0.589	6.525	0.0903
7	0.324	2.983	0.1086
8	0.075	5.206	0.0144
9	1.020	16.065	0.0635
10	0.423	5.025	0.0842
11	0.516	3.583	0.1440
12	0.393	2.959	0.1328
13	1.996	11.419	0.1748
14	1.848	8.610	0.2146
15[a]	0.308	0.562	0.5480
16	0.681	6.829	0.0997
17	2.072	11.107	0.1865
18	0.483	6.528	0.0740
19	0.236	3.174	0.0744
20[a]	—	0.580	NA
21[a]	5.390	5.741	0.9389
22	0.126	1.547	0.0814
23	1.413	33.307	0.0424
24	0.563	6.852	0.0822
25	1.268	5.384	0.2355

[a] These three samples were not included in the calculation of the statistical information summarized in Table 1.

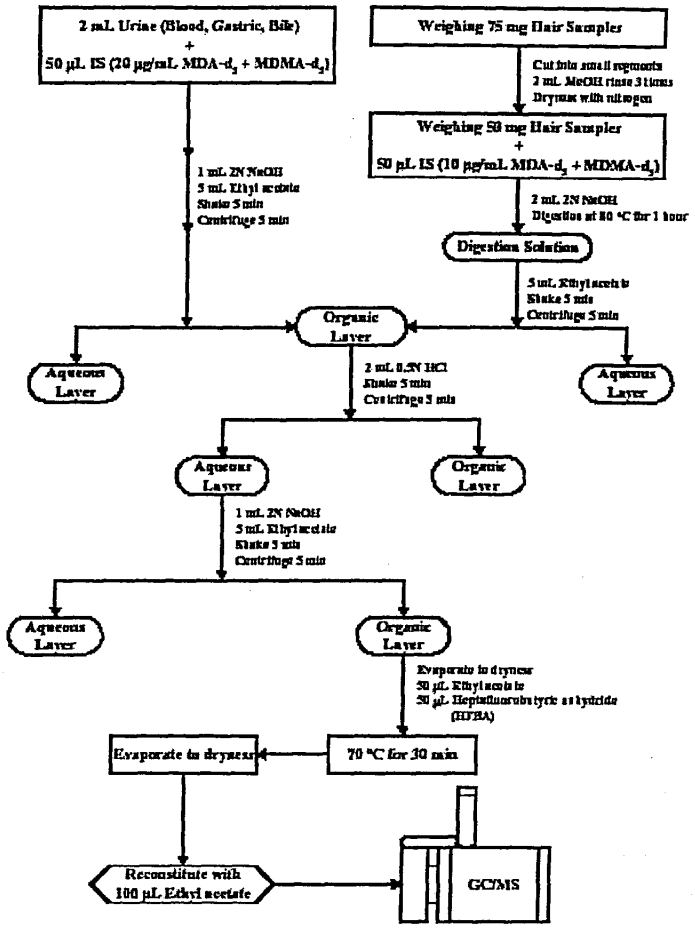

Figure 1. Sample preparation scheme for the analysis of MDMA and MDA.

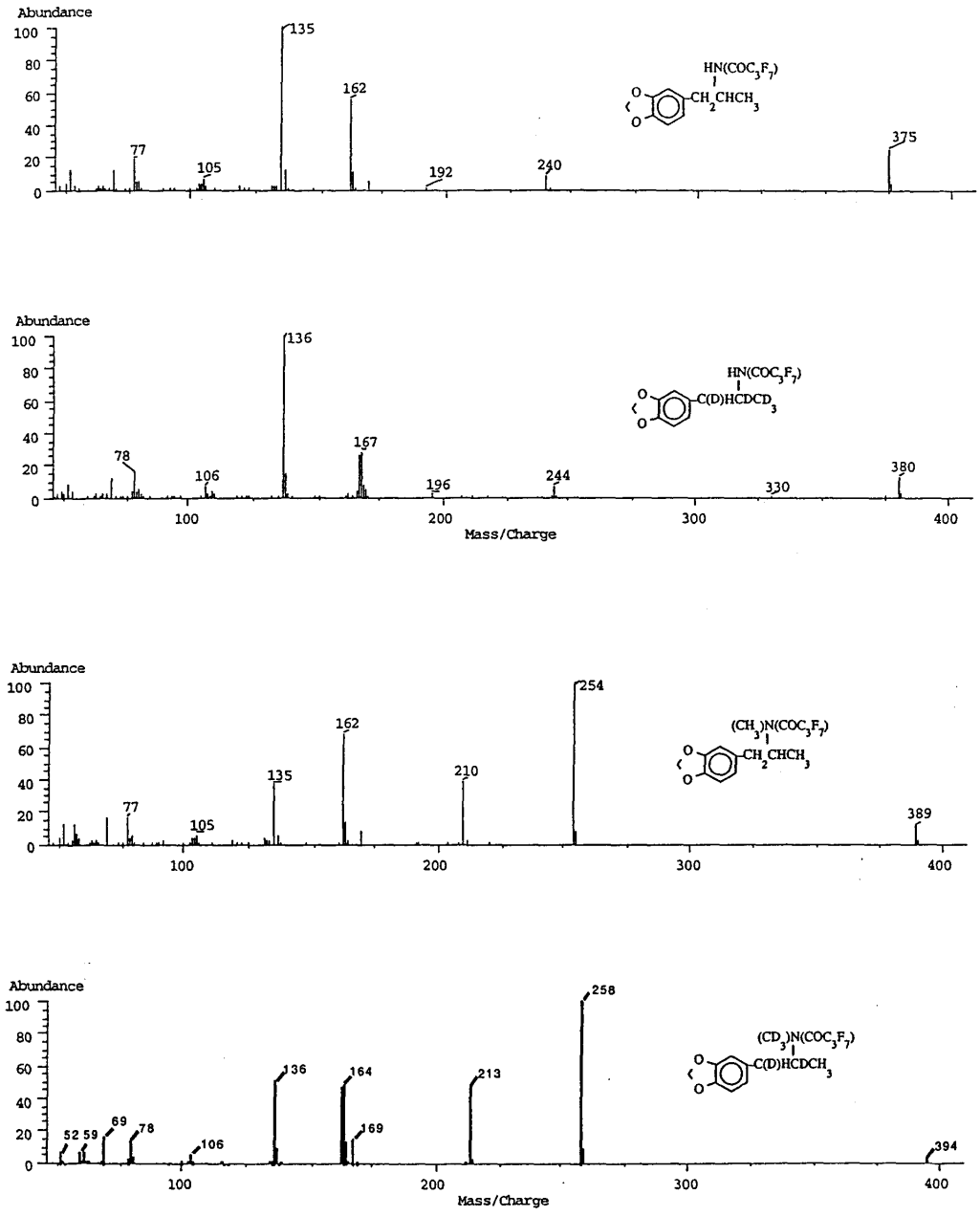

Figure 2. Mass spectra and structures of analytes and internal standards: MDA/MDA-d_5, and MDMA/MDMA-d_5 (all as HFB-derivatives).

附件二

Journal of Analytical Toxicology, Vol. 27, October 2003

Performance Characteristics of Selected Immunoassays for Preliminary Test of 3,4-Methylenedioxymethamphetamine, Methamphetamine, and Related Drugs in Urine Specimens

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Abstract

Eight commercially available immunoassays for amphetamines (DRI® Amphetamines, CEDIA® DAU Amphetamines-Semiquantitative, EMIT® d.a.u. Monoclonal Amphetamine/Methamphetamine, Synchron CX® Systems AMPH, TDx®/TDxFLx® Amphetamine/Methamphetamine II, CEDIA Amphetamines/Ecstasy, COBAS® INTEGRA Amphetamines, and Abuscreen® OnLine HS Amphetamine/MDMA) are evaluated for their effectiveness in serving as the preliminary test methodology for the analysis of 3,4-methylenedioxymethamphetamine/3,4-methylenedioxyamphetamine (MDMA/MDA) and methamphetamine/amphetamine (MA/AM). Standard solutions (in urine matrix) of MDMA, MDA, MA, and AM are used to determine these immunoassays' reactivities (or cross-reactivities) toward these compounds of interest. Case specimens containing MDMA/MDA and MA/AM are also used to study the correlations of the apparent immunoassay MDMA (or MA) concentrations and the gas chromatographic–mass spectrometric concentrations of these compounds. Data resulting from this study suggest that CEDIA Amphetamines/Ecstasy can best predict the concentrations of MDMA and MA in case specimens and can also detect the presence of MDMA at low levels, whereas Abuscreen OnLine HS Amphetamine/MDMA can detect both MDMA and MA at low concentrations.

Introduction

Along with heroin, methamphetamine (MA) has long been one of the two most commonly abused drugs in Taiwan. With recent popularity of "club" drugs, especially ecstasy (3,4-methylenedioxymethamphetamine, MDMA), among the younger population (1), we are interested in better understanding the performance characteristics and effectiveness of various commercially available immunoassays for the preliminary identification of urine specimens that contain MA or MDMA and their metabolites, amphetamine (AM) and 3,4-methylenedioxyamphetamine (MDA), respectively.

There have been several reported studies addressing the performance characteristics of immunoassays for amphetamines. For example, in 1988, Ruangyuttikarn and Moody (2) reported low MDMA cross-reactivity of the three immunoassays (Abuscreen RIA, EMIT, and TDx) that adapted MA/AM as the targeted analytes. In 1990, Kunsman et al. (3) reported that MDMA cross-reactivity exhibited by EMIT d.a.u. Monoclonal Amphetamine/Methamphetamine was generally low, while that exhibited by TDx Amphetamine/Methamphetamine was high (118%) at low concentration (150 ng/mL), but unacceptably low (18%) at a higher level (10 µg/mL). Zhao et al. (4) recently evaluated TDx, EMIT II, CEDIA DAU Amphetamines, and five different Abuscreen OnLine formats and concluded that TDx Amphetamine/Methamphetamine II and Abuscreen OnLine HS Amphetamine/MDMA displayed greater detection sensitivity for MDMA. Very recently, scientists from the manufacturer reported the performance characteristics of Multiplex CEDIA Amphetamines/Ecstasy (5), which incorporates three monoclonal antibodies specific for AM, MA, and MDMA.

This study is characterized by 1. the evaluation of an extended list of reagents under the same settings; 2. the emphasis on the effectiveness in simultaneous detection of MDMA/MDA and MA/AM by these immunoassays; and 3. the correlation of case specimen data derived from these immunoassays and gas chromatographic–mass spectrometric (GC–MS) procedures.

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Materials and Methods

Immunoassay reagents and analyzers

Immunoassays and analyzers used in this study are summarized in Table I. All immunoassay reagents were prepared and used according to the instructions provided by respective manufacturers for the specified analyzers used for the analysis. Name abbreviations of these immunoassays as listed in Table I shall be used for discussion hereafter.

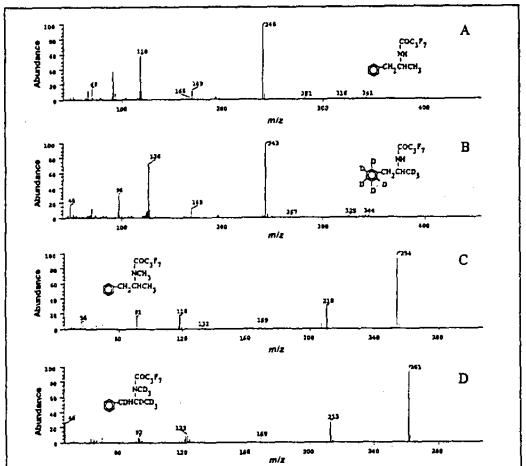

Figure 1. Full-scan mass spectra of AM (A), AM-d_8 (B), MA (C), and MA-d_8 (D) (all as HFB-derivatives).

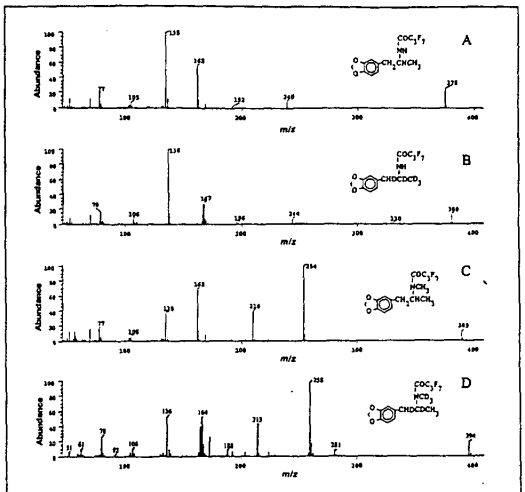

Figure 2. Full-scan mass spectra of MDA (A), MDA-d_5 (B), MDMA (C), and MDMA-d_5 (D) (all as HFB-derivatives).

Table I. Amphetamines Immunoassays and Analyzers

Immunoassay (abbreviation)	Calibrator (Suggested cutoff)	Manufacturer	Reagent insert date	Analyzer*
DRI Amphetamines (DRI-Amp)	*d*-Methamphetamine (1000 ng/mL)	Diagnostic Reagents, Inc. (Sunnyvale, CA)	May 1999	Hitachi 7060
CEDIA DAU Amphetamines-Semiquantitative (CEDIA-Amp)	*d*-Methamphetamine (1000 ng/mL)	Microgenics Co. (Fremont, CA)	December 1999	Hitachi 7070
EMIT d.a.u. Monoclonal Amphetamine/Methamphetamine (EMIT-Amp)	*d*-Methamphetamine (1000 ng/mL)	Syva Co. (Cupertino, CA)	1999	Hitachi 7060
Synchron CX Systems AMPH (Synchron-CX-Amp)	*d*-Methamphetamine (1000 ng/mL)	Beckman Coulter, Inc. (Fullerton, CA)	May 2000	Hitachi 7070
TDx/TDxFLx Amphetamine/ Methamphetamine II (TDx-Amp)	*d*-Amphetamine (1000 ng/mL)	Abbott Laboratories (Abbott Park, IL)	January 1996	Axsym
CEDIA Amphetamines/Ecstasy (CEDIA-Amp/MDMA)	*d*-Methamphetamine (1000 ng/mL)	Microgenics Co. (Fremont, CA)	May 2001	Hitachi 7060
COBAS INTEGRA Amphetamines (COBAS-Amp)	*d*-Amphetamine (500 ng/mL)	Roche Diagnostics Co. (Indianapolis, IN)	May 1998	COBAS INTEGRA 700
Abuscreen OnLine HS Amphetamine/MDMA (OnLine-Amp/MAMA)	MDMA (300 ng/mL)	Roche Diagnostics Co. (Indianapolis, IN)	March 2000	Hitachi 7060

* Hitachi: Hitachi High-Technogies Co. (Tokyo, Japan); Axsym: Abbott Laboratories (Abbott Park, IL); COBAS INTEGRA: Roche Instrument Center AG (Rotkreuz, Switzerland).

Drug standards and case specimens

Solutions used for cross-reactivity studies were prepared by diluting drug standards (*d,l*-MA, *d,l*-AM, MDMA, MDA, and MDEA) in methanol (1 mg/mL) purchased from Cerilliant Co. (formerly Radian, Austin, TX) with drug-free urine. MDMA from this source (Cerilliant) was diluted and used as the calibrator for CEDIA Amp/MDMA (see further detail in the Results and Discussion section), in addition to the use of *d*-MA that was provided by the manufacturer. Internal standards (MA-d_8, AM-d_8, MDMA-d_5, MDA-d_5) in methanol (1 mg/mL) were also purchased from Radian/Cerilliant Co.

Twenty-eight MDMA/MDA- and 32 MA/AM-containing urine specimens used in this study were case specimens scheduled for disposal. These specimens were used to study the correlation of data derived from immunoassay and GC–MS tests. Since the linearity ranges of the immunoassays are limited and test results are most relevant around the "cutoff" concentration, these specimens were diluted with appropriate amount of drug-free urine so that the concentration of the targeted analytes were at the vicinity of the adapted GC–MS cutoff concentration (6) (see the Results and Discussion section for further detail).

Table II. Ions Monitored for All Amphetamines Tested by GC–MS

Compounds	Ion (*m/z*)*
Amphetamine/Amphetamine-d_8	240, 117, 118; 243, 126
Methamphetamine/Methamphetamine-d_8	254, 210, 118; 261, 213
MDA/MDA-d_5	162, 240, 375; 167, 244
MDMA/MDMA-d_5	254, 210, 162; 258, 213

* Quantitation ions are underlined.

Immunoassay

The procedures described in respective reagent package inserts were followed using calibrators provided by respective manufacturers. However, an additional test was performed for CEDIA Amp/MDMA reagent, in which MDMA was used as the calibrator (see the Results and Discussion section for further discussion).

For cross-reactivity studies, *d,l*-MA/*d,l*-AM and MDMA/MDA/MDEA were generally evaluated at the 300–2000 and 300–1000 ng/mL concentration ranges, respectively.

GC–MS procedures

For specimen pretreatment, 2-mL urine aliquots were extracted with ethyl acetate under basic conditions. Heptafluorobutyric anhydride (HFBA) (Aldrich, St. Louis, MO) was used to derivatize the analytes (AM, MA, MDMA, and MDA) and deuterated internal standards (MA-d_8, AM-d_8, MDMA-d_5, and MDA-d_5).

GC–MS analysis was performed on an HP 6890 GC interfaced to an HP 5973N MS (Agilent, Palo Alto, CA). A 30-m × 0.25-mm (0.25-µm film thickness) HP-5MS capillary column (Agilent, Wilmington, DE) was used for this study. The GC column was operated at an initial temperature of 90°C for 1 min, programmed to 280°C at 15°C/min with a 3-min hold at the final temperature. Ions monitored and those adapted for the quantitation of AM, MA, MDMA, and MDA are shown in Table II. Full-scan mass spectra of these compounds and their deuterated analogues are shown in Figures 1 and 2. Confirming the presence of a specific analyte is based on the widely adapted criteria, that is, presence of the monitored ions at the acceptable retention time (within ± 2% of that established by the standards) and two independent intensity ratios of the three ions monitored (within ± 20% of those established by the standards).

Table III. Immunoassay Cross-Reactivities toward MDMA, MDA, MDEA, AM, and MA

		% Cross-reactivity*				
Immunoassay	Calibrator	MDMA	MDA	MDEA	*d,l*-AM	*d,l*-AM
DRI-Amp	*d*-AM	111–44	99–51	69–25	66–61	81–54
CEDIA-Amp	*d*-MA	68–57	0–0	25–20	N.E.†	N.E.†
EMIT-Amp	*d*-MA	7–46	214–175	0–0	223–194	0–66
Synchron-CX-Amp	*d*-MA	100–49	73–58	39–17	90–70	92–57
TDx-Amp	*d*-AM	93–82	103–92	76–48	111–79	52–72
COBAS-Amp	*d*-AM	124–72	48–38	42–24	60–58	128–65
OnLine-Amp/MDMA	MDMA	142–111	100–75	45–24	355–227	197–125
CEDIA-Amp/MDMA	*d*-MA	173–319‡	98–123	1214§	78–57	65–57
CEDIA-Amp/MDMA	MDMA	100#	63–36	148–68	41–26	40–29

* Except those noted, the concentration ranges tested were 300–1000 ng/mL for MDMA/MDA/MDEA and 300–2000 ng/mL for *d,l*-AM/*d,l*-MA. Typically, higher cross-reactivity values were observed when the drug concentrations were at the lower end (300 ng/mL).
† N.E.: Not evaluated.
‡ Concentration range tested: 200–300 ng/mL. At higher concentrations, responses exceed the analyzer's response range.
§ Concentration tested: 300 ng/mL. Responses at higher concentrations exceed the analyzer's response range.
# Standard MDMA from the same source was used for calibration and cross-reactivity study.

Results and Discussion

Cross-reactivity studies of MA, AM, MDMA, MDA, and MDEA

Reactivity data of MA, AM, MDMA, MDA, MDEA from the immunoassays that were evaluated are summarized in Table III. These

values were calculated by dividing the observed immunoassay concentrations by the true concentrations of the standards used for the study and the results are expressed as percentages. Because the calibrators were typically *d*-enantiomers (*d*-AM or *d*-MA) and the prepared solutions used for evaluation were typically racemic mixtures (*d,l*-AM and *d,l*-MA), the observed cross-reactivity data were typically not 100%, even when the calibrators and the standards were the same compound at the same concentration.

Data shown in Table III indicate the following performance characteristics: 1. Cross-reactivity data are typically lower when the compounds examined are at the higher concentration (see Figures 3 and 4 for this trend). 2. With the exception of CEDIA-Amp/MDMA, immunoassays included in this study have lower cross-reactivity to MDEA than MDMA. 3. CEDIA-Amp/MDMA (*d*-MA as the calibrator) and OnLine-Amp/MDMA have the highest (> 100%) detectability of MDMA and MDA. OnLine-Amp/MDMA also has high cross-reactivities toward *d,l*-MA and *d,l*-AM. 4. Among those designed for the detection of MA/AM, the following immunoassays have ≥ 50% cross-reactivity toward MDMA and MDA: DRI-Amp, Synchron-CX-Amp, and TDx-Amp. The following two immunoassays have ≥ 50% cross-reactivity toward MDMA, but not MDA: CEDIA-Amp, COBAS-Amp. [Fifty percent cross-reactivity is the proposed minimum acceptable value in the draft guidelines of the National Laboratory Certification Program (7)]. EMIT-Amp has high cross-reactivity toward MDA, but is probably not effective if used for the detection of MDMA at the 500 ng/mL level.

Immunoassay and GC–MS data derived from MDMA/MDA- and MA/AM-containing urine specimens

Because the use of various commercially available immunoassays for the preliminary test of MA/AM has been well established, the primary emphasis of this study is on characterizing the performance of these immunoassays for detecting MDMA. Selected assays that exhibited potential for detecting MDMA are evaluated further to understand their performance characteristics in the analysis of MA/AM. Immunoassays that can be successfully used for preliminary test of both MDMA/MDA and MA/AM are identified.

Performance characteristics of immunoassays in the analysis of MDMA. Shown in Table IV are GC–MS and immunoassay apparent MDMA concentration data derived from 28 MDMA/MDA-containing specimens. Visual inspection of these data indicate that the apparent MDMA concentrations derived from the following reagents are lower than the true (GC–MS) concentrations: DRI-Amp, CEDIA-Amp, EMIT-Amp, and Synchron-CX-Amp. These immunoassays are designed for preliminary test of MA/AM with lower cross-reactivities toward MDMA/MDA. Thus, data derived from these reagents are not examined further.

Data derived from the remaining reagents (TDx-Amp, COBAS-Amp, OnLine-Amp/MDMA, CEDIA-Amp/MDMA (MDMA as calibrator) show significant responses toward MDMA/MDA and are examined further. Specifically, apparent MDMA concentrations derived from these reagents are plotted against the GC–MS MDMA concentration as shown in Figures 5A–D. The same scale for the *y*- and *x*-axes are used in all plots to facilitate visual comparison. Data derived from eight specimens (see the third footnote in Table IV), of which data for certain immunoassays are not available (exceeding the upper response limit), are excluded all together to ensure that comparisons are based on plots generated by the identical set of specimens.

The four plots shown in Figure 5 reveal the following performance characteristics:

Correlation of immunoassays and GC–MS data. Results derived from CEDIA-Amp/MDMA (MDMA as calibrator) (Figure 5D) and COBAS-Amp (Figure 5B) exhibit the best correlations

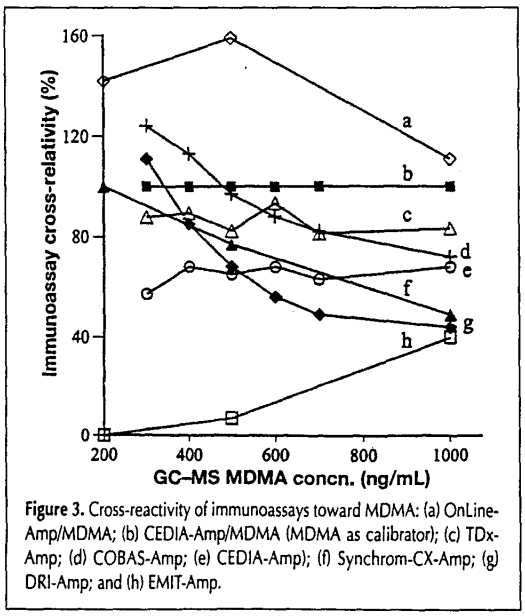

Figure 3. Cross-reactivity of immunoassays toward MDMA: (a) OnLine-Amp/MDMA; (b) CEDIA-Amp/MDMA (MDMA as calibrator); (c) TDx-Amp; (d) COBAS-Amp; (e) CEDIA-Amp); (f) Synchrom-CX-Amp; (g) DRI-Amp; and (h) EMIT-Amp.

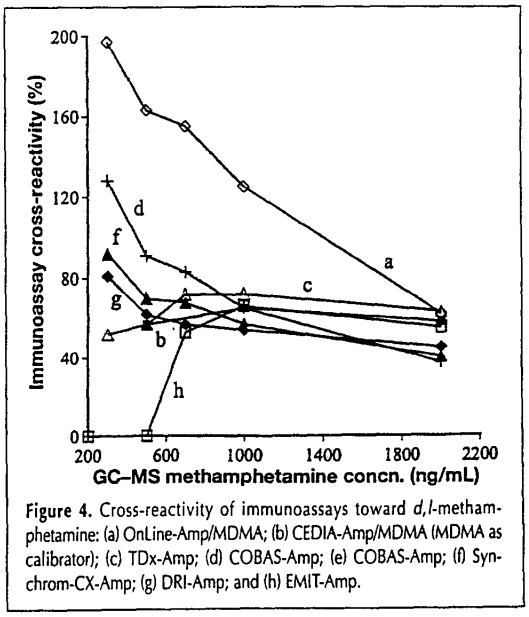

Figure 4. Cross-reactivity of immunoassays toward *d,l*-methamphetamine: (a) OnLine-Amp/MDMA; (b) CEDIA-Amp/MDMA (MDMA as calibrator); (c) TDx-Amp; (d) COBAS-Amp; (e) COBAS-Amp; (f) Synchrom-CX-Amp; (g) DRI-Amp; and (h) EMIT-Amp.

with GC–MS MDMA concentrations (r^2 = 0.5117 and 0.4143). Apparent MDMA concentrations equivalent to 500 ng/mL MDMA for these two immunoassays are approximately 543 ng/mL and 475 ng/mL, respectively. This is an indication of limited cross-reactivities of these two immunoassays toward MDMA metabolites, such as MDA, an observation consistent with cross-reactivity data shown in Table III.

OnLine-Amp/MDMA (Figure 5C) exhibits poor correlation (r^2 = 0.0876) with GC–MS MDMA concentration. Apparent MDMA concentrations equivalent to 500 ng/mL MDMA for this immunoassay is approximately 723 ng/mL. This is most likely due to this reagent's higher response toward MDMA and higher cross-reactivities toward MDA and other MDMA metabolites present in the specimens. This is consistent with the higher cross-reactivity (100–75% for OnLine-Amp/MDMA of this reagent toward MDA shown in Table III.

The performance of TDx-Amp (Figure 5A) falls between the characteristics exhibited by CEDIA-Amp/MDMA (and COBAS-Amp) and OnLine-Amp/MDMA.

Detectivity. CEDIA-Amp/MDMA (*d*-MA as calibrator) (data not shown) and OnLine-Amp/MDMA (Figure 5C) exhibit the highest responses toward MDMA. These assays will detect more specimens containing MDMA and metabolites than the other methods.

Performance characteristics of immunoassays for analyzing MA. Shown in Table V are GC–MS and immunoassay apparent MA concentration data derived from 32 MA/AM-containing specimens. Only the data derived from the four immunoassays (TDx-Amp, COBAS-Amp, OnLine-Amp/MDMA, CEDIA-Amp/MDMA), which show potentially effectiveness for the analysis of MDMA, are evaluated. Specifically, apparent MA concentrations derived from these immunoassays are plotted against the GC–MS MA concentration as shown in Figures 6A–D. Again, the same set of *x*- and *y*-axis are used for all plots to facilitate visual comparison. Data derived from eight specimens (footnoted in Table V), for which data for certain immunoassays are not available or are of dubious nature, are excluded all together to ensure that comparisons are based on plots generated from the identical set of specimens.

The four plots shown in Figure 6 reveal the following perfor-

Table IV. GC–MS and Immunoassay Data for MDMA/MDA-Containing Specimens

Spec. no.	GC–MS concn. MDMA/MDA (ng/mL)	Immunoassay apparent targeted analyte concentration							
		DRI-Amp	CEDIA-Amp	EMIT-Amp	Synchron-CX-Amp	TDx-Amp	COBAS-Amp	OnLine-Amp/MDMA	CEDIA-Amp/MDMA*
392	425/5.3	303	140	4	310	400	436	636	384
393	431/3.8	291	220	20	360	506	465	570	479
394	576/10	327	273	8	373	592	540	1006	640
395	544/8.8	361	311	15	370	686	566	746	670
396	783/6.1	320	298	11	350	547	546	642	661
397	654/4.7	376	376	13	371	689	600	867	719
398	732/3.7	369	403	30	439	844	647	917	750
399	403/40	358	222	12	477	743	496	825	536
400‡	658/14	425	522	25	518	928	> 666†	1184	980
401	682/14	250	137	3	264	478	405	555	473
402	718/6.1	348	374	49	445	639	563	815	831
403	623/3.2	374	356	33	472	716	575	1114	694
404	733/17	344	334	107	450	777	566	753	690
405	654/2.8	360	415	90	475	730	538	855	731
406	469/8.8	280	177	5	274	434	380	649	467
407	464/13	317	253	7	341	574	464	647	568
DG-408‡	688/29	374	437	198	534	1161	> 666†	1093	678
409‡	777/85	552	838	300	644	1630	> 666†	1283	1684
410	594/24	333	241	77	350	783	519	867	557
DF-382	546/21	285	207	4	224	434	435	565	509
DF-383	561/27	276	192	6	308	477	451	586	525
DF-394‡	373/44	636	706	1099	705	2390	> 666†	3055	1678
DF-385‡	487/15	313	244	83	365	611	515	–§	559
DF-387	513/2.7	286	308	38	318	529	499	768	675
DF-388‡	604/434	>†	1776	153	1867	>†	> 666†	>†	>†
DF-389	401/15	265	181	14	353	396	395	660	411
DH-423‡	711/61	1435	2370	2169	1299	5365	> 666†	2808	>†
DH-424‡	535/64	–§	–§	>†	–§	>†	> 666†	29593	>†

* These data were obtained using MDMA as the calibrator. With the exception of two specimens, responses exceeded instrument measurement limit when using *d*-MA as the calibrator.
† Responses exceed the analyzer's response range.
‡ Data derived from these specimens are not plotted in Figure 5 (see text for reasons).
§ Data not available.

mance characteristics: 1. Results derived from CEDIA-Amp/MDMA (*d-MA as calibrator*) (Figure 6D) and TDx-Amp (Figure 6A) show the best correlations with GC–MS MA concentration (r^2 = 0.2222 and 0.207, respectively). Apparent MA concentrations equivalent to 500 ng/mL MA for these two immunoassays are approximately 1146 ng/mL and 1420 ng/mL, respectively. 2. OnLine-Amp/MDMA (Figure 6C) exhibits the highest response, but shows poorer correlation (r^2 = 0.1616) with GC–MS MA concentration. Apparent MA concentration equivalent to 500 ng/mL MA for this immunoassay is approximately 2582 ng/mL. This is most likely due to this reagent's higher response toward MA and higher cross-reactivities toward AM and other MA metabolites present in the specimens. This is consistent with the high response to MA (355–227%) and high cross-reactivity with AM (197–125%) shown in Table III. Thus, the presence of MA (and its metabolites) can be most effective detected by this reagent. However, because of the poor correlation of the immunoassay and GC–MS data, this reagent will not be very effective in predicting the concentration of MA.

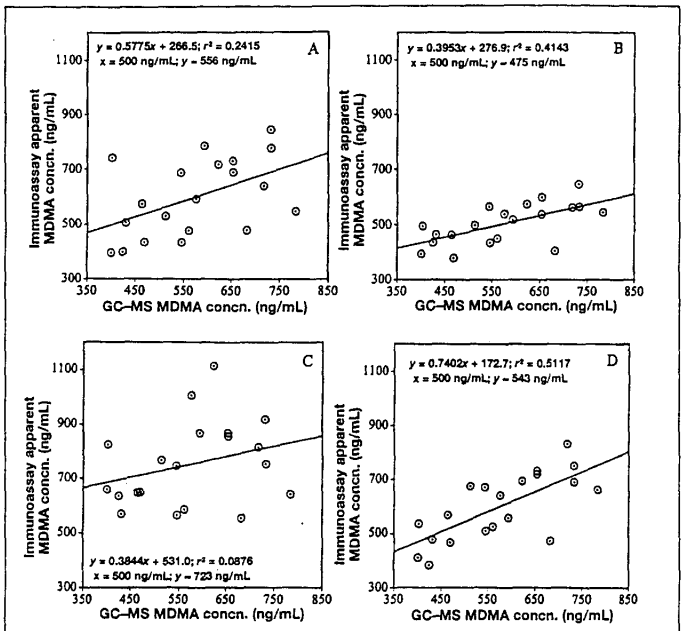

Figure 5. Correlation of GC–MS MDMA concentration and apparent MDMA concentration derived from four immunoassays: TDx-Amp (A), COBAS-Amp (B), OnLine-Amp/MDMA (C), CEDIA-Amp/MDMA (D).

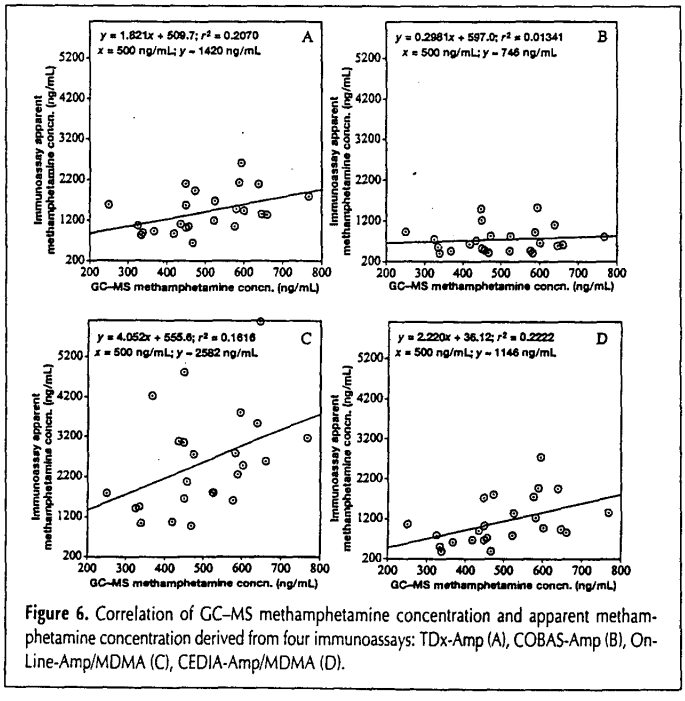

Figure 6. Correlation of GC–MS methamphetamine concentration and apparent methamphetamine concentration derived from four immunoassays: TDx-Amp (A), COBAS-Amp (B), OnLine-Amp/MDMA (C), CEDIA-Amp/MDMA (D).

Effectiveness in identifying specimens "positive" for MDMA and MA

Case specimen data shown in Tables IV and V can be used to examine these immunoassays' effectiveness in identifying specimens that are "positive" (above an adapted cutoff) for MDMA/MDA and MA/AM, respectively. "False-negative" and "false-positive" rates will obviously vary when different "cutoffs" are applied to immunoassay data (i.e., when a lower immunoassay cutoff is adapted, the false-positive rate will increase, and the corresponding false-negative rate will decrease, and vice versa). We have studied this issue in depth (8) and adapted an approach that can best evaluate the "effectiveness" of the immunoassays compared. Specifically, immunoassay and GC–MS data from a significant number of case specimens containing appropriate concentrations of the analytes of interest (and their metabolites) are first collected. Regression analyses of these data are performed to arrive at an apparent analyte concentration for each immunoassay that is equivalent to a specific analyte concentration as determined by GC–MS. Immunoassay apparent analyte concentrations thereby derived are then adapted as these immunoassays' respective cutoffs, based on which false-positive and false-negative rates are most evenly distributed. These concentrations are shown in respective plots in Figures 5 and 6.

With this approach and adapting 500 ng/mL MDMA (or MA) as the GC–MS cutoffs, the regression analyses are illustrated in Figures 5 and 6, and the resulting immunoassay cutoffs, and the false-positive and false-negative rates

for the immunoassays examined are shown in Table VI. Among the four immunoassays shown in Table VI, the immunoassay's apparent MDMA or MA concentrations, corresponding to 500 ng/mL MDMA or MA, respectively, derived from OnLine-Amp/MDMA are the highest. Thus, OnLine-Amp/MDMA generates the highest responses for both MDMA and MA, that is, detecting the presence of MDMA and MA at their lowest concentrations. (It should be noted, however, if *d*-MA is used as the calibrator, CEDIA-Amp/MDMA may generate an even higher immunoassay concentration equivalent to 500 ng/mL MDMA, that is, detecting the presence of MDMA even at a lower concentrations.)

In terms of the numbers of false-negative and false-positive results generated, CEDIA-Amp/MDMA (MDMA as the calibrator for testing MDMA and *d*-MA as the calibrator for testing MA) appears to be the most effective immunoassay for the preliminary tests of MDMA and MA.

Conclusions

Immunoassays' performance can be characterized by examining 1. their cross-reactivities toward compounds that are related to the adapted calibrators and 2. the correlation of the resulting apparent immunoassay analyte concentrations with the analyte concentrations derived from GC–MS analysis. Prepared solutions in urine matrix are used for the former studies, whereas analyte-containing case specimens, which include normal distributions of the analytes and related metabolites, are needed (and used in this study) to derive meaningful results for the latter studies.

Among the immunoassays evaluated, many are effective for the preliminary test of MA/AM-containing specimens. CEDIA-Amp/MDMA appears to be most effective in serving as the preliminary test methodology for both MDMA/MDA and MA/AM (MDMA as the calibrator for testing MDMA and *d*-MA as the cal-

Table V. GC–MS and Immunoassay Data for MA/AM-Containing Specimens

Spec. no.	GC–MS concn. MA/AM (ng/mL)	Immunoassay apparent targeted analyte concentration							CEDIA-Amp/MDMA‡	
		DRI-Amp	CEDIA-Amp†	EMIT-Amp	Synchron-CX-Amp	TDx-Amp	COBAS-Amp	OnLine-Amp/MDMA	MDMA	*d*-MA
11	250/194	666		1115	945	1589	932	1790	332	1069
12	522/86.4	627		1236	848	1200	465	1827	360	790
13	646/106	768		1062	858	1360	590	6081	339	947
14*	285/25.8	221		241	160	100	72	173	81	54
15	456/83.1	594		1069	708	1057	483	2091	326	729
16	338/88.4	410		603	649	894	409	1050	251	392
17	449/246	683		1709	1035	1584	1220	4818	354	1035
18*	360/46.6	385		529	483	496	277	960	207	270
19*	541/62.2	303		0	181	162	92	149	155	104
20	638/159	1295		1914	1190	2096	1113	3550	475	1967
21	449/85.4	578		797	761	1025	526	1668	283	676
23	334/98.6	432		612	525	836	559	1464	264	510
24	576/55.1	694		625	685	1061	470	1614	305	1757
25*	640/108	1479		2011	1094	2190	677	5880	779	22,774
26	588/142	1345		1653	1130	2135	924	2270	440	1976
27*	636/72.7	381		217	369	442	313	1847	213	201
28	418/106	524		649	638	876	631	1089	301	677
29	448/212	1070		1496	1085	2106	1500	3060	421	1733
30*	455/22.8	288		0	119	96	57	139	114	68
31	660/109	860		1069	873	1348	618	2600	372	860
32	594/247	1606		1794	1273	2614	1534	3830	491	2745
33	435/111	668		741	802	1116	725	3090	333	912
36	467/83.4	434		376	491	647	420	981	242	394
37	601/104	748		911	927	1451	660	2496	358	977
38	767/125	937		1641	964	1793	812	3180	391	1359
39	325/121	498		1195	712	1075	753	1425	310	793
40	525/135	835		953	973	1683	828	1810	369	1348
41*	767/47.1	§§		1856	1168	2161	618	8290	455	2034
42	367/61.4	527		421	765	935	460	4230	289	614
43	473/67.5	1322		1536	1148	1938	830	2770	467	1813
44*	388/58.6	320		224	187	145	45	148	136	115
45	581/44.2	938		1062	1015	1493	414	2800	370	1233

* Data derived from these specimens are not plotted in Figure 6 (see text for reasons).
† Not studied.
‡ Data obtained using methamphetamine as the calibrator are plotted in Figure 6. Data obtained using MDMA as the calibrator are lower than true (GC–MS) MDMA concentration and are not discussed further.
§ Data not available.

Table VI. Effectiveness of Four MDMA-Responsive Immunoassays in Identifying Specimens Containing MDMA or MA ≥ 500 ng/mL

Cutoff, specimen no., analyte, pos./neg. rate	TDx-Amp	COBAS-Amp	OnLine-Amp/MDMA	CEDIA-Amp/MDMA*	
				MDMA	*d*-MA
MDMA/MDA					
Immunoassay cutoff (ng/mL)	560	480	730	550	—
Specimens with valid data†	28	28	27	28	—
Number of false negatives	5	3	4	3	—
Immunoassay positive/GC–MS positive‡	19/15	20/17	18/16	20/17	—
(% false positive)	(21%)	(15%)	(11%)	(15%)	
MA/AM					
Immunoassay cutoff (ng/mL)	1420	750	2590	—	1150
Specimens with valid data§	32	32	32	—	32
Number of false negatives	6	10	7	—	6
Immunoassay positive/GC–MS positive‡	13/9	10/5	13/8	—	11/9
(% false positive)	(31%)	(50%)	(38%)	—	(18%)

* MDMA and *d*-MA were used as the calibrators for the analysis of MDMA and MA, respectively.
† Out of the 28 specimens listed in Table IV, for the reason stated in the text, only 20 were adapted for regression analysis to derive the immunoassay apparent MDMA concentrations (adapted as cutoffs for respective immunoassays) that are equivalent to 500 ng/mL MDMA. However, all valid data derived from each specific immunoassay are used to derive data in this table for that specific immunoassay.
‡ The following example illustrates how the numbers of "immunoassay positive", "GC–MS positive", and "% false positive" are derived. 19/25 (21%): Out of 19 specimens found positive by the immunoassay, 15 were confirmed positive by GC–MS positive; thus, 21% (4 out of 19) were false positive. Since different IAs may identify different specimens and different number of specimens positive, the number of "GC–MS positive" out of the specimens, that have been identified as positive by respective immunoassays, may vary.
§ Out of the 32 specimens listed in Table V, for the reason stated in the text, only 24 were adapted for regression analysis to derive the immunoassay apparent MA concentrations (adapted as cutoffs for respective immunoassays) that are equivalent to 500 ng/mL MA. However, all valid data derived from specific immunoassay are used to derive data in this table for that specific immunoassay.

ibrator for testing MA). CEDIA-Amp/MDMA (*d*-MA as the calibrator) and OnLine-Amp/MDMA can detect the presence of MDMA and MA, respectively, at the lowest concentrations.

Acknowledgments

The completion of this study and the manuscript would not have been possible without the assistance received from the following sources: financial support provided by the National Bureau of Controlled Drugs, Department of Health, Taipei, Taiwan; laboratory analysis assisted by the following individual and laboratories: Mr. M.-K. Kuang, Ms. S.-F. Chuang, Ms. R.-F. Chang, Dr. Chin-Cheng Chou, (Taiwanese) Aeronautic Medicine Center for Civil Aeronautics Administration and Clinical Toxicology Department at Taipei Veterans General Hospital; and financial support provided to Ray H. Liu by the (Taiwanese) National Science Council (NSC-90-2811-B-043D-001) and (Taiwanese) Ministry of Justice's Institute of Forensic Medicine.

Comments from Mr. Lorenzo Ajel of Microgenics were also very helpful.

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