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March 10, 2017

Honorable William H. Pryor
Acting Chair
United States Sentencing Commission
One Columbus Circle, N.E.
Suite 2-500, South Lobby
Washington, D.C. 20002-8002

Re: MDMA/Ecstasy, MDPV, Methyone, Mephedrone, JWH-018, AM-2201

Dear Judge Pryor:

While Defenders opposed the Commission's proposal to make synthetic cannabinoids and cathinones a priority this amendment cycle, Defenders appreciate that the Commission is not trying to act on this complicated issue this year, and instead is engaged in a two-year study. Although we remain concerned that even a two-year study period may not be sufficient to adequately address these "understudied substances,"¹ we are pleased that the Commission is not considering these drugs in isolation, and is also examining its approach to MDMA.

When the Commission decided in August 2016 to undertake a study of MDMA/Ecstasy, synthetic cannabinoids and synthetic cathinones, it said that it would consider "any amendments to the Guidelines Manual that may be appropriate in light of the information obtained from such a study."² Because of the numerous issues that have arisen with drugs not listed in the drug equivalency table, as well as drugs already listed, Defenders believe that the Commission should study not only the specific controlled substances listed in the request for comment, but also other aspects of the drug guideline. Among the issues Defenders encourage the Commission to study are the following: the appropriate role of drug quantity and how direct harms of the drugs at issue should be measured; amending the factors that govern a court's consideration of analogues and controlled substances not referenced in §2D1.1;³ including an invited departure when the

¹ Congressional Research Service, *Synthetic Drugs: Overview and Issues for Congress* (May 3, 2016) (citing Office of National Drug Control Policy, *National Drug Control Strategy 2013*, at 10).

² USSC, Notice of Final Priorities, 81 Fed. Reg. 58004 (Aug. 24, 2016).

³ Those factors are listed in §2D1.1, comment. (n.6).

potency of an analogue is less than the “most closely related” substance referenced in the guideline; and re-examining the drug equivalency for THC.⁴ Our specific comments follow.

I. The Guidelines’ Focus on Drug Quantity Does Not Serve the Purposes of Sentencing and Should be Revisited

Without more guidance on how the Commission intends the drug guidelines’ emphasis on drug type and quantity to advance the statutory purposes of sentencing, it is difficult to analyze and comment on how the guidelines should treat offenses involving MDMA, synthetic cathinones and synthetic cannabinoids. Judges and scholars have long cited the excessive weight given drug quantity as the drug guidelines’ chief flaw.⁵ Defenders and others have urged the Commission to review how the drug guidelines are linked to mandatory minimums through the Drug Quantity Table (“DQT”) and whether this linkage advances any purpose of sentencing.⁶ Research and

⁴ See also Statement of Molly Roth Before the U.S. Sentencing Comm’n, Washington, D.C., at 28–30 (Mar. 13, 2014) (suggesting invited downward departures for (1) “when the weight of the mixture or substance containing a detectable amount of a drug over-represents the actual dosages that are involved and the seriousness of the offense”; and (2) “when quantity overstates the defendant’s role in the offense”).

⁵ See, e.g., Judicial Conference of the United States, *1995 Annual Report of the JCUS to the U.S. Sentencing Commission* 2 (1995) (“[T]he Judicial Conference . . . encourages the Commission to study the wisdom of drug sentencing guidelines which are driven virtually exclusively by the quantity or weight of the drugs involved.”); General Accounting Office, *Sentencing Guidelines: Central Questions Remain Unanswered* (1992) (harshness and inflexibility of drug guideline most frequent problem cited by interviewees); Peter Reuter & Jonathan P. Caulkins, *Redefining the Goals of National Drug Policy: Recommendations from a Working Group*, 85 Am. J. Pub. Health 1059, 1062 (1995) (reporting recommendations of a RAND corporation working group, which concluded: “The U.S. Sentencing Commission should review its guidelines to allow more attention to the gravity of the offense and not simply to the quantity of the drug.”); *United States v. Diaz*, 2013 WL 322243, at *1 (E.D.N.Y. Jan. 28, 2013) (discussing that “drug type and quantity” are “poor proxies for culpability” and encouraging Commission to “de-link” §2D1.1 from “weight-driven mandatory minimum sentences”).

⁶ See, e.g., Statement of Michael Nachmanoff, Federal Public Defender for the Eastern District of Virginia, Before the U.S. Sentencing Comm’n, Washington, D.C. (May 27, 2010); Statement of Julia O’Connell, Federal Public Defender for the Eastern and Northern Districts of Oklahoma, Before the U.S. Sentencing Comm’n, Austin, Tex. (Nov. 19, 2009); Statement of Nicholas T. Drees, Federal Public Defender for the Northern and Southern Districts of Iowa, Before the U.S. Sentencing Comm’n, Denver, Col. (Oct. 21, 2009) (citing numerous problems with drug trafficking guidelines and urging major revision); Statement of James Skuthan, Before the U. S. Sentencing Comm’n, Washington, D.C. (Mar. 17, 2011); Statement of Molly Roth, Before the U. S. Sentencing Comm’n, Washington, D.C. (Mar. 13, 2014). See also Letter from Paul G. Cassell, Chair, Committee on Criminal Law of the Judicial Conference of the United States, to the Honorable Ricardo Hinojosa, Chair, U.S. Sentencing Comm’n, at

analyses have shown that determinations of drug quantity are often arbitrary and capricious, are estimated from hearsay or other unreliable evidence,⁷ are easily manipulated by law enforcement agents and confidential informants,⁸ and result in “false precision.”⁹ For the Commission to rationalize sentencing for particular substances such as the synthetics currently being studied, it should reconsider its prior decisions.

The Commission has cited different rationales for the DQT at different times. Congress’s intention that “[d]rug quantity would serve as a proxy to identify those traffickers of greatest concern” has long been cited.¹⁰ The mandatory minimums have been described as creating a “two-tiered penalty structure for discrete categories of drug traffickers” that would differentiate among “major” and “serious” traffickers.¹¹ But research both inside and outside the Commission has amply demonstrated that the quantity thresholds found in the statutes, and incorporated into the DQT, do a poor job of making this differentiation and often result in guideline recommendations exceeding the levels Congress intended for various functional roles.¹²

3 (Mar. 16, 2007) (reviewing history); *Mandatory Minimums and Unintended Consequences*, Hearing Before the Subcommittee on Crime, Terrorism, and Homeland Security of the Committee on the Judiciary, House of Representatives, 111th Cong. 34 (July 14, 2009) (statement of Hon. Julie E. Carnes) (reviewing history), <http://judiciary.house.gov/hearings/pdf/Carnes090714.pdf>; *Mandatory Minimum Sentencing Laws—The Issues*, Hearing Before the Subcommittee on Crime, Terrorism, and Homeland Security of the Committee on the Judiciary, House of Representatives, 110th Cong. (June 26, 2007) (statement of Hon. Paul Cassell), <http://judiciary.house.gov/hearings/June2007/Cassell070626.pdf>; *United States v. Booker: One Year Later—Chaos or Status Quo?*, Hearing Before the Subcommittee on Crime, Terrorism, and Homeland Security of the Committee on the Judiciary, House of Representatives, 109th Cong. 59-65 (Mar. 16, 2006) (statement of Hon. Paul J. Cassell).

⁷ Estimates of quantities that were not actually seized, that were under negotiation, etc., inevitably are unreliable approximations. See, e.g., *United States v. Quinn*, 472 F. Supp. 2d 104, 111 (D. Mass. 2007).

⁸ Jeffrey L. Fisher, *When Discretion Leads to Distortion: Recognizing Pre-Arrest Sentence-Manipulation Claims under the Federal Sentencing Guidelines*, 94 Mich. L. Rev. 2385 (1996); Eric P. Berlin, *The Federal Sentencing Guidelines’ Failure to Eliminate Sentencing Disparity: Governmental Manipulations Before Arrest*, 1993 Wis. L. Rev. 187 (1993).

⁹ Justice Stephen Breyer, *Federal Sentencing Guidelines Revisited*, 11 Fed. Sent’g Rep. 180 (Feb. 1999).

¹⁰ USSC, *Cocaine and Federal Sentencing Policy* 118 (1995).

¹¹ USSC, *Report to Congress: Mandatory Minimum Penalties in the Federal Criminal Justice System* 24, n.144, 145 (2011).

¹² See USSC, *Cocaine and Federal Sentencing Policy* 42-49 (2002) (showing drug mixture quantity fails to closely track role and other important facets of offense seriousness); USSC, *Cocaine and Federal*

Commission analyses also have sometimes discussed: 1) methods of ingestion of various forms of a drug and collateral harms of use; 2) the prevalence of use among various demographic populations, or involvement of these groups in trafficking; 3) possible deterrent effects of various penalty levels; 4) the effects of penalties on incentives for investigation and prosecution of particular controlled substance violations; 5) the effect of drug penalties on the prison population; and 6) Congressional intent or sentiment, as expressed through legislation or formal and informal communications.

The Commission has sometimes sought to assign thresholds to various drugs in the DQT based on the relative harmfulness of a drug. Discussion of drug harms was central to the Commission's reports on cocaine sentencing, which reviewed a wide range of empirical and medical evidence on the relative harmfulness of powder and crack cocaine.¹³ To determine or evaluate the thresholds for other drugs, Commission reports on MDMA ("ecstasy")¹⁴ and steroids¹⁵ have all reviewed various harms caused by these drugs and their trafficking.

Unfortunately, the Commission's previous harmfulness comparisons have been ad hoc and not well tailored to sentencing policy making. Prevalence of use and other indirect harms not fairly attributable to defendants have been confounded with the relevant harms. The types of harms taken into account have been inconsistent, as has consideration of the important matter of dosage weight.¹⁶ And while Commission reports have sometimes corrected mistaken ideas about the

Sentencing Policy 28-29, Fig. 2-12 (2007) (showing large numbers of low-level crack and powder cocaine offenders exposed to harsh penalties intended for more serious offenders); USSC, *Mandatory Minimum Penalties* App. A, Fig. D-2 (nearly half of drug couriers (49.6%), and most street level dealers (65.5%) are attributed with quantities of drugs qualifying them for a mandatory minimum penalty). *See also* Hon. Patti B. Saris, *A Generational Shift for Federal Drug Sentences*, 52 Am. Crim. L. Rev. 1, 12-13 (2015).

¹³ USSC, *Cocaine and Federal Sentencing Policy* (1995, 2002, 2007).

¹⁴ USSC, *2001 Report to the Congress: MDMA Drug Offense, Explanation of Recent Guideline Amendments* 6-10 (2001).

¹⁵ USSC, *2006 Steroids Report* 23-26 (2006).

¹⁶ Paul J Hofer, *Ranking Drug Harms for Sentencing Policy* (May 2015), http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2612654.

harmfulness of a particular drug,¹⁷ the reports themselves have sometimes relied on evidence that was later proven mistaken, most notably in regard to the neurotoxicity of MDMA.¹⁸

While there are several possible theories of the relation of drug type and weight to statutory purposes, the current DQT reflects an assortment of thresholds, special rules, and piecemeal actions by Congress and the Commission that lack any clear rationale. In addition to the thresholds, ratios, and definitions in the mandatory minimum statutes to which the Commission sometimes feels bound,¹⁹ the drug guideline has been subject to statutory directives concerning MDMA/ecstasy, methamphetamine, amphetamine, powder and crack cocaine, anabolic steroids, hydrocodone, and oxycodone, precursor drugs like ephedrine, and so-called “date-rape” drugs like flunitrazepam and GHB. The prison terms associated with quantities of many types of drugs were chosen in part based on aggravating factors thought to be associated with those drugs, such as violence (crack), or use by role models such as athletes (anabolic steroids), or marketing to youth (ecstasy). Through the years, aggravating upward offense level adjustments were added to the guideline to reflect some of these harms, and a variety of other factors, without any reduction in the quantity-based base offense level.

¹⁷ A perceived epidemic of “crack babies” contributed to the harsh treatment of crack cocaine under the Anti-Drug Abuse Act of 1986 and the original guidelines. The Commission later found that “research indicates that the negative effects from prenatal exposure to cocaine, in fact, are significantly less severe than previously believed.” USSC, *Cocaine and Federal Sentencing Policy* 68 (2007).

¹⁸ George A. Ricaurte et al., *Severe Dopaminergic Neurotoxicity in Primates After a Common Recreational Dose Regimen of MDMA (“Ecstasy”)*, 297 *Science* 2260–63 (2002); Ricaurte et al., *Retraction*, 301 *Science* 1479 (2003); Editorial, *Ecstasy’s After-effects*, 425 *Nature* 223 (2003) (“The retracted paper left the public with the impression that ecstasy is far more hazardous than it may actually turn out to be.”), <http://www.nature.com/nature/journal/v425/n6955/full/425223a.html>.

¹⁹ The Commission has occasionally departed from statutory thresholds and definitions for guideline purposes, and has been upheld by the courts. Anomalies surrounding sentencing for LSD, where the dosage weight of the active ingredient is miniscule, led the Commission to depart from Congress’s weighing approach for LSD and instead base punishment on standardized dosage units. *See* USSG App. C, Amend. 488 (Nov. 1, 1993); USSG §2D1.1(c), Notes to Drug Quantity Table (G). The Commission’s dosage-based method was subsequently accepted by courts for guideline application, but not for statutory minimum penalties. *See Neal v. United States*, 516 U.S. 284 (1996). Special rules for other situations were also developed, such as standardized weights for marijuana, USSG §2D1.1(c), Notes to Drug Quantity Table (E), and instructions to allow unsmokable, rain- or sea-soaked marijuana to dry before weighing. USSG §2D1.1, comment (n.1).

II. The Commission's Study Should Focus on Direct Harms

A. Issues for Comment

While the Commission seeks broad comment on a number of issues, we encourage the Commission to focus on the relative direct harms of the drugs under consideration.²⁰ The Commission's questions about the "potential for addiction and abuse" and "the pattern of abuse and harms associated with abuse" appropriately focus on direct harms of the drugs, which can contribute to the seriousness of the offense and the culpability of a defendant.

We are concerned, however, by the Commission's apparent interest in broader issues that are already accounted for, or irrelevant to the purposes of sentencing an individual defendant. For example, the request for comment on "the patterns of trafficking" suggests the Commission is interested in considering issues beyond direct harms. We do not believe that the marijuana equivalency of a drug for purposes of the DQT should reflect that the drug is sometimes marketed and sold by means of a computer service, when the drug guideline contains a specific adjustment for such cases.²¹ Nor should marijuana equivalencies be affected by the popularity of a drug with minors, when sale to or involvement of minors in a drug offense are treated elsewhere in the statutes and guidelines.²² Even the overall or increasing popularity of a drug are not strictly relevant to the harms caused by a particular defendant.²³ Increasing the sentence of a drug defendant because many other people also sell the drug is like punishing a thief for crimes committed by other thieves, and undermines just desert rationale for the drug guidelines' consideration of type and quantity.

In addition, some of the considerations in the request for comment misdirect attention to matters only loosely or largely unrelated to the question of harm, while elevating arcane technical matters to an importance unjustified by their relation to the purposes of sentencing. The request

²⁰ See generally Hofer, *supra* note 16.

²¹ USSG §2D1.1(b)(7). Congress and the Commission made an analogous mistake for many years by allowing the quantity ratio of crack to be affected by the drug's association with firearms, when firearms and violence are taken into account elsewhere under the guidelines in cases where they are relevant.

²² See USSG §2D1.1(b)(15)(B); §2D1.2 (Drug Offenses Occurring Near Protected Locations or Involving Underage or Pregnant Individuals); 21 U.S.C. § 859 (Distribution to persons under age twenty-one).

²³ When the Commission lengthened sentences for MDMA, some Commissioners noted its use had been increasing in the preceding years. But the increased penalties were never changed in response to decreases in use. Moreover, no evidence shows that marginal sentence increases have a deterrent effect. Andrew von Hirsch et al., *Criminal Deterrence and Sentence Severity: An Analysis of Recent Research* (1999); Michael Tonry, *Purposes and Functions of Sentencing*, 34 *Crime & Justice: A Review of Research* 28–29 (2006).

for comment states: “In determining the marijuana equivalencies for specific controlled substances, the Commission has considered, among other things, the chemical structure” of the drug. This is echoed in §2D1.1, comment. n.6, which begins by directing courts’ attention to “(A) [w]hether the controlled substance not referenced in §2D1.1 has a chemical structure that is substantially similar to a controlled substance referenced in this guideline.” We suggest that extensive analysis of the chemical structure of a controlled substance is both wasteful and misguided so long as it lacks any clear connection to a sentencing purpose. Rather than establish fixed equivalencies for unlisted substances, or direct courts to hear testimony from chemists, we believe the more urgent need is for the Commission to re-evaluate the logic of this inquiry. Similarity of chemical structure is relevant only insofar as it affects “the pharmacological effects . . . , potential for addiction and abuse . . . and harms associated with abuse.”²⁴

The Commission’s own analysis, as well as that of the courts, would be improved by emphasizing data on a particular drug’s direct harms, which depends relatively little, if at all, on technical details of its chemical structure. Data on direct harms are available from emergency room visits, poison control centers, coroner’s findings, and other sources. Sensationalized, isolated, anecdotes are not helpful, and can distort assessments of harm through operation of the availability heuristic and neglect of base rates. But medical and public health data, considered in the context of rates of overall use, might provide a framework for rational assessment of the relative risk of various harms from different drugs. Such data seem to us more relevant to the sentencing purpose of proportionate sentencing based on a new drug’s harmfulness than do technical details of chemical structure.

We are also unclear how “the legislative and scheduling history” is relevant to establishing rational sentencing policy for drug traffickers.²⁵ Indeed, it has often been a source of distortion. Considering the “patterns of trafficking and harms associated with trafficking” also risks contaminating marijuana equivalencies in the DQT with considerations addressed elsewhere in the guidelines or irrelevant to the sentence deserved by a particular defendant. While we address the Commission’s questions about how these substances are “manufactured, distributed, possessed, and used” and “[h]ow these offenses and offenders compare with other drug offenses and drug offenders,” we believe the focus of the Commission’s study should be on any direct harms caused by the drugs themselves, and how those harms compare to other drugs.

B. Clarifying the Principle of Proportionality to Harms

Severity of punishment proportionate to the harms caused by an offense can be a sound sentencing principle, and could be related to the DQT’s emphasis on drug type and quantity. But

²⁴ USSC, Issues for Comment, 81 Fed. Reg. 92021 (Dec. 19, 2016).

²⁵ *Id.*

several aspects of the treatment of drug type and quantity under the guidelines undermine that principle. These include inconsistent attention to typical dosage weight and drug purity.

1. Typical dosage weight

The third consideration that Note 6 directs courts to consider is “[w]hether a lesser or greater quantity of the controlled substance not referenced in §2D1.1 is needed to produce a substantially similar effect on the central nervous system as a controlled substance referenced in this guideline.” We agree that typical effective dosage quantity is relevant to proportional sentences in a system in which drug type and quantity are central.

Broadly speaking, typical dosage weight has influenced the statutes and guidelines. It is, however, hard to explain how the widely varying quantities of different drugs yield the same offense level under the DQT. For example, the minimum quantity of drugs qualifying defendants for offense level 24 varies from 1 gram for LSD to 100,000 grams for marijuana.²⁶ The same level applies to 100 grams of heroin, 500 grams of powder cocaine, 28 grams of cocaine base, 50 grams of methamphetamine, or 5 grams of methamphetamine (actual).²⁷ Along with differences in the harmfulness of different drugs (at least as perceived by policymakers), some of these radical differences must be related to differences in the weight of a typical effective dose.

Penalties based on drug quantity cannot be made proportionate without considering typical effective dose. It is therefore surprising that the guidelines are not more clear and consistent in their attention to typical dosage size. The Commission’s method for determining offense levels for LSD is explicitly dose-based.²⁸ Courts are also directed to use typical dose weights whenever the number of pills or capsules is known but total weight is not.²⁹ For other drugs, however, the guidelines ignore dosage weights and fail to treat equivalent doses of similar drugs similarly. This inconsistency is acknowledged in a note to the Drug Equivalency Table: “[b]ecause of the statutory equivalences, the ratios in the Drug Equivalency Tables do not necessarily reflect dosages based on pharmacological equivalents.”³⁰ Most importantly, as discussed below, the mandatory minimum statutes inclusion of “mixtures and substances containing a detectable amount” of a drug—and the Commission’s adoption of that standard beyond the requirements of the statutes—is guaranteed to make much of drug sentencing needlessly arbitrary and disparate.

²⁶ USSG §2D1.1(c), Notes to Drug Quantity Table (G).

²⁷ USSG §2D1.1(c)(8).

²⁸ USSG §2D1.1(c), Notes to Drug Quantity Table (G).

²⁹ USSG §2D1.1, comment. (n.9).

³⁰ USSG §2D1.1, comment. (n.8(b)).

In practice, dose amounts vary depending on many factors, including the purity of the mixture, the experience and tolerance of users, the mode of ingestion, and the desired intensity and length of intoxication. Even in commercial pharmaceuticals, there is often no universal dose. If the Commission remains committed to drug sentencing based largely on drug type and quantity, these problems cannot be avoided and a standard is needed. The best standard seems to be “typical effective dose.” Drug researcher Robert Gabel has described this as “the estimated quantity for an average healthy 70-kg human who has not developed tolerance to the substance and who does not have residues of the substance in the body from previous administrations.”³¹

A variety of knowledgeable sources provide information on typical doses for the most common illegal drugs. The sentencing guidelines themselves contain a table with typical dosage weights for several drugs.³² Notably, the Commission’s standardized dosage weight for LSD includes both the weight of the drug itself and a carrier medium.³³ For other drugs, academic,³⁴ government,³⁵ and inter-governmental sources are available,³⁶ as is a well-known website that discusses user experiences and reports typical recreational doses for many drugs.³⁷ These provide guidance for many drugs, including the synthetic drugs of concern here.

2. Purity

The issue of dosage weight in the drug guidelines is confused further by the inconsistent treatment of drug purity. The history of this issue is interesting and perplexing. When statutory penalties were first linked to drug quantities in the Controlled Substances Penalties Amendments

³¹ Robert S. Gabel, *Comparison of Acute Lethal Toxicity of Commonly Abused Psychoactive Substances*, 99 *Addiction* 686, 690, tbl. 1. footnote (2004).

³² USSG §2D1.1, comment. (n.9).

³³ USSG §2D1.1, comment. (n.10).

³⁴ See, e.g., Gabel, *supra* note 31 (compilation of dosage evidence); Federation of American Scientists, Comment on the Proposed Changes to MDMA (“Ecstasy”) Penalties to the U.S. Sentencing Comm’n (Mar. 2001).

³⁵ Drug Enforcement Administration, *Drug Trafficking in the United States* (Sept. 2001); Office of National Drug Control Policy, *Pulse Check: Trends in Drug Abuse November 2001*, at 11 (Nov. 2001), <https://static.prisonpolicy.org/scans/fall2001.pdf>; National Highway Traffic Administration, *Drugs and Human Performance Fact Sheets*, <https://one.nhtsa.gov/people/injury/research/job185drugs/methamphetamine.htm>.

³⁶ The European Monitoring Centre for Drugs and Drug Addiction provides “scientifically sound descriptions of drugs,” including typical dosage amount, www.emcdda.europa.eu/drug-profiles.

³⁷ The Vaults of Erowid, www.erowid.org.

Act of 1984,³⁸ the weight of the pure drug was used. The Parole Commission guidelines in effect at the time of the Sentencing Reform Act also measured offense seriousness based on the amount of pure drug. The weight of any mixture or substance was discounted by its purity. “For example, ten grams of a mixture containing heroin at 50 percent purity and twenty grams of a mixture containing heroin at 25 percent purity were each graded as equivalent to five grams of heroin at 100 percent purity because each of the mixtures contained the same quantity of heroin (five grams).”³⁹ The Parole Commission’s practice makes sense—similar amounts of the active ingredient, with similar potential for harm, are treated similarly.

For reasons that are far from clear, Congress departed from its previous approach and Parole Commission practice in the Anti-Drug Abuse Act and made the new mandatory penalties contingent on the entire weight of any “mixture or substance containing a detectable amount” of a drug.⁴⁰ This was guaranteed to add an arbitrary element to weight determinations, with widely varying amounts of actual drugs treated similarly. It also had the perverse effect of increasing punishments for persons lower in the distribution chain, where dilution of drugs is more common.⁴¹

The legislative record is largely unhelpful as to why Congress made this change. The House Committee that described the two-tiered system discussed earlier—the rationale that links quantity to a defendant’s role rather than amount of harm done—called the inclusion of inert ingredients in the weight a “market-oriented approach.” “The quantity is based on the minimum [weight of the mixture including the drugs] that might be controlled . . . by a trafficker in a high place in the . . . distribution chain.”⁴² The evidence upon which Congress based these thresholds is unclear.

While Congress’s reasons for including inert substances in the weight determining penalties are unclear, in its initial deliberations over the drug trafficking guideline “some concern was

³⁸ Pub. L. No. 98-473, 98 Stat. 2068 (1984).

³⁹ Ronnie Skotkin, *The Development of the Federal Sentencing Guidelines for Drug Trafficking Offenses*, 26 *Crim. Law Bull.* 50, 52 (1990) (describing Parole Commission guideline approach, and Sentencing Commission’s abandonment of guideline development research upon passage of the Anti-Drug Abuse Act of 1986).

⁴⁰ *See* 21 U.S.C. § 841.

⁴¹ *See* Institute for Defense Analyses & Office of National Drug Control Policy, *Price and Purity of Illicit Drugs: 1981-2007* (2008) (reporting purity of seizures involving four quantity ranges of various drugs), <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB2010104175.xhtml>.

⁴² H.R. Rep. No. 99-845, 99th Cong., at 11–12 (1986).

expressed within the Commission that requiring the courts to establish both the weight and purity of a mixture . . . might unduly complicate the sentencing process.”⁴³ The Commission never decided the issue, however, because the Anti-drug Abuse Act intervened and the Commission largely followed the statutory approach. Information on drug purity is available to courts in standard lab reports.⁴⁴ But this information may be excluded from pre-sentence reports because it is ordinarily irrelevant to guideline calculation.

However, in another arbitrary twist for some drugs, such as PCP and methamphetamine, the statutes and guidelines establish different quantity thresholds for “actual” weights, which require courts to rely on lab reports and consider purity information.⁴⁵ As best we can determine, in consultation with Commission staff, no one knows why Congress chose to treat these particular drugs differently. The best rationale we have been able to reconstruct—that Congress sought to punish smokable, and therefore more addictive, forms of these drugs more harshly—was undone by Commission amendments.⁴⁶ The failure of the guidelines to discount the weight of inactive substances mixed with the active ingredient is especially important for synthetic cannabinoids, given that they, like LSD, for which the Commission developed special dosage-based procedures, are usually mixed with substances that dwarf the weight of the active ingredient.

⁴³ Skotkin, *supra* note 39, at 52.

⁴⁴ See, e.g., National Forensic Science Technology Center, *A Simplified Guide to Forensic Drug Chemistry* 4 (discussing how confirmatory tests “may also include quantitative analysis of the sample to determine the amount, or purity, of the illegal substance”). See also USSG §2D1.1, comment. (n.27(C)) (inviting upward departure for “unusually high purity”).

⁴⁵ USSG §2D1.1(c), Notes to Drug Quantity Table (B).

⁴⁶ The Anti-Drug Abuse Act of 1986 infamously treated powder and crack cocaine differently, and the Commission later argued that this could be justified because crack was more addictive due to its mode of ingestion. USSC, *Cocaine and Federal Sentencing Policy* 92 (2002) (“The Commission agrees . . . that differences in the intrinsic harms posed by the two drugs (e.g., addictiveness) should be reflected in different base offense penalties and therefore different quantity-based penalties.”). In the Crime Control Act of 1990 Congress showed a similar concern regarding “smokable crystal methamphetamine.”

This rationale for different treatment of actual weight and mixtures is lost, however, under Note B to the Drug Quantity Table. Rather than weigh the drugs in whatever form they were trafficked, and use the quantities from the statutes and guidelines that correspond to that form, Note B directs courts to use a comparative approach. Drugs in pure form are weighed and the offense level from the DQT is determined. Drugs in a mixture are weighed, and then purity is considered, to determine the offense level applicable to the actual drugs within the mixture. The note then instructs courts to use “whichever is greater.”

3. The Drugs at Issue

The implications of this history and analysis for the drugs that are the subject of this request for comment are daunting. Unless the Commission is willing to revisit fundamental aspects of the guidelines' treatment of drug type and quantity, or develop special procedures as it has for LSD and other situations where issues of dosage and purity distort quantity determinations, sentencing for these drugs will reflect and perpetuate the absurdities and injustices of drug sentencing in the guidelines era. Instead of continuing to direct judges to engage in technical, but irrelevant fact finding to calculate equivalencies of intricate, but meaningless precision, the Commission should reconsider and explain how drug type and quantity might advance rational, proportionate punishment.

The absurdity and injustice of the current DQT system is well-illustrated by marijuana, THC, and the synthetic cannabinoids at issue here. The Commission recognized long ago that including the weight, for example, of sea water in bales of marijuana that had been thrown overboard arbitrarily increases punishment for some unfortunate defendants in ways that are unrelated to proportionate punishment or the purposes of sentencing. Commentary to the DQT instructed courts to allow unsmokable rain- or sea-soaked marijuana to dry before weighing, as well to exclude the weight of certain other unusable and inert mixtures and substances.⁴⁷ But the fundamental error of basing punishment on quantities that are only loosely, or even inversely, related to dosage amounts and ultimate harm remained endemic to the DQT system.

Further veneers of false precision were created by extensive commentary that developed around the DQT. Lengthy tables of "drug equivalencies" initially appear aimed at some sort of precision until no consistent and rational answer exists to the question: Equivalent in terms of what? Not typical dosage amounts; not equivalent harms; in some cases, equivalent only to the ratios of the thresholds in the mandatory minimum statutes, whose origins are either unknown or known to be unrelated to the sentencing purpose of proportionate punishment based on harm.⁴⁸ The basis for some equivalencies has been shown to be misguided and inaccurate and leads to absurd results.⁴⁹

⁴⁷ USSG §2D1.1, comment (n.1). In response to circuit conflicts and disparate practices in the district courts, the Commission also eventually directed courts not to count fiberglass, beeswax, or other materials from which a drug must be separated before it can be consumed, and to not count laboratory wastewater containing unusable trace amounts of a drug. USSG App. C, Amend. 484 (Nov 1, 1993).

⁴⁸ USSG §2D1.1, comment (n.8(a)); comment (n.8(b)) ("*Note*: Because of the statutory equivalences, the ratios in the Drug Equivalency Tables do not necessarily reflect dosages based on pharmacological equivalents.").

⁴⁹ For example, when the Commission established the equivalency for pseudoephedrine, the active ingredient in Sudafed, it was intended to "correspond to the quantity of controlled substance that reasonably could have been manufactured using the quantity" of precursor involved. *See* USSG App. C,

The principle psychoactive ingredient in marijuana is the cannabinoid THC, which is produced and sold by prescription in a pharmaceutical formulation, and is also produced and sold illicitly for the recreation and unsupervised self-medication market. The Drug Equivalency Table at Note 8(d) provides an equivalency for a mixture or substance containing either organic or synthetic THC of 167 grams of marijuana per 1 gram of THC. Under this equivalency, for a given amount of marijuana to contain a similar dose of its primary active ingredient THC, the marijuana would need to contain about 0.6 percent THC.

The most recent data on range and average potencies of marijuana on the illicit market today shows this is wildly inaccurate. The University of Mississippi's Potency Monitoring Project tests marijuana seized by the DEA in all 50 states, using a validated gas chromatography with flame ionization detector method. While the potency of different marijuana strains differs significantly, the average potency in 2014 was about 12 percent.⁵⁰ This means that to similarly punish THC and marijuana crimes that yield similar numbers of doses for the most typical potencies of marijuana, the equivalency between THC and marijuana should be about 8 grams of marijuana per 1 gram of THC, not 167 grams. Under the current equivalencies, THC defendants are sentenced as if they trafficked in amounts of marijuana about 20 times too large.

This problem is exacerbated for synthetic cannabinoids. If courts sentencing synthetic cannabinoid defendants determine that THC is the most similar listed drug, and determine the marijuana equivalency using the weight of both the synthetic cannabinoid and the inert plant material onto which it has been sprayed, the dosage comparison is off by another large multiple. Research shows that concentrations of synthetic cannabinoids in "spice" and similar mixtures are in the range of one to two percent by weight. This means the current marijuana equivalency for THC when used in "spice" cases "equates" one dose of synthetic cannabinoid to between 1000 to 2000 doses of marijuana.

Amend. 625, Reason for Amendment (Nov. 1, 2001). Apparently based on "information provided by the Drug Enforcement Administration (DEA) that the typical yield of these substances for clandestine laboratories is 50 to 75 percent" the Commission settled on a yield ratio for pseudoephedrine of 50 percent. *Id.* Thus, the marijuana equivalency for pseudoephedrine in the Chemical Quantity Table at guideline §2D1.11 (which operates similarly to the DQT) is twice that of actual methamphetamine. Subsequent research has suggested that yields of 50 percent meth from pseudoephedrine are not the norm in the haphazard conditions of clandestine labs. Nile Bremer & Robin J. Woolery, *The Yield of Methamphetamine Unreacted Precursor and Birch By-Product with the Lithium-Ammonia Reduction Method as Employed in Clandestine Laboratories*, Iowa Division of Criminal Investigation Laboratory (1999). As a result, the punishment for pseudoephedrine is typically more severe than for the methamphetamine that could be made from it. After the reduction of crack cocaine sentences in the Fair Sentencing Act of 2010, meth (actual) is arguably the most severely punished major drug, but because of this questionable equivalency, Sudafed is punished even more severely.

⁵⁰ Mahmoud A. ElSohly et al., *Changes in Cannabis Potency Over the Last 2 Decades (1995–2014): Analysis of Current Data in the United States*, 79 *Biological Psychiatry* 613 (2016).

The ranges of marijuana quantities at each level of the DQT are far too small to mitigate this error in dosage equivalency. The tops of the quantity range at various levels of the DQT are two to four times larger than the bottom, i.e., a multiple of two to four.⁵¹ If the dosage equivalency is off by a multiple of one to two thousand, this results in synthetic cannabinoid defendants receiving base offense levels that are many levels too high. This discrepancy results in recommended guideline sentences even for pure THC defendants that exceed dosage-similar marijuana offenses, ranging from several months at the lower end of the Sentencing Table to nearly a decade at the top.⁵²

Research appears to have implications for determining a more appropriate marijuana equivalency for synthetic cannabinoids. Some evidence shows that some synthetic cannabinoids are more potent in their pure form than pure THC.⁵³ However, synthetic cannabinoids are usually sprayed onto plant material before consumption. All of the problems with the guidelines' treatment of "mixtures or substances" come into play, and there is real danger that retailers of "spice" or other smokable, highly diluted forms of the drug could face penalties, due to the

⁵¹ See, e.g., USSG §2D1.1(c)(2) (level 36 – at least 30,000KG but less than 90,000KG of Marijuana; level 30 – at least 100KG but less than 400KG of Marijuana; level 16 – at least 20KG but less than 40KG of Marijuana).

⁵² Of the 176 drug defendants in the past ten years whose primary drug type was organic or synthetic THC, 9.9 percent were held accountable for 539 kg or more—the amount that places one at level 38 in the DQT. (A defendant with 539kg currently receives a marijuana equivalency of 90,000 kg.; $539\text{kg} \times 167\text{g} = 90,013\text{kg}$.) If the THC:marijuana equivalency was set instead at the ratio reflecting the best current national data on average marijuana potency, it would be about 1:8. Using the accurate ratio, the marijuana equivalency for 539kg of THC would be 4,312kg ($539\text{kg} \times 8\text{kg} = 4,312\text{kg}$). This would result in a base offense level under the DQT of 32, not 38. For a first-time defendant with no other guideline adjustments, the minimum of the recommended guideline range would be 121 months of imprisonment instead of 235 months. In other words, the current guideline nearly doubles the sentence length due solely to the current marijuana equivalency, which misrepresents the available current data about comparable dosage amounts. The nearly ten percent of THC defendants who were held accountable for more than 539kg would already receive the maximum base offense level of 38 under the DQT, so their quantity differences are not taken into account by the guidelines. The available Commission data do not indicate whether the substance involved in the offense was pure organic or synthetic THC, or a mixture or substance, like spice, which sometimes has been held to be most similar to THC. As noted in the text, for defendants sentenced for "spice"-type drugs that were held to be most similar to THC, use of the current marijuana equivalencies yields base offense levels, and resulting sentences, that are even more egregious from a dosage perspective.

⁵³ Brian Burrows et.al., *Synthetic Cannabinoids: a Summary of Selected Phenomena With Respect to Behavioral Pharmacology and Abuse Liability in Handbook of Cannabis and Related Pathologies* 691–99 (2017).

weight of the inert ingredients, that exceed those of manufacturers or high-level distributors where drugs are confiscated in pure form.

Some research shows that concentrations of synthetic cannabinoids in “spice” and similar mixtures are significantly *lower* than typical concentrations of THC in marihuana. This, of course, may more than offset any differences in potency of the pure form. One study found that concentrations were in the range of one to two percent by weight, compared to the recent 12 percent average concentration of THC in marihuana noted above.⁵⁴ Of course, concentrations are not consistent among brands, or even among different batches of the same brand. A U.N. report found that the same product might vary not only in amount but also in the type of synthetic cannabinoid used. Some samples were found to be unadulterated with any type of synthetic cannabinoid whatsoever.⁵⁵

III. The Commission Should Consider Amending §2D1.1, comment. (n.6), to Improve Guidance on Determining the Drug Equivalency for Analogues and Controlled Substances Not Referenced in §2D1.1

A. The Factors a Court Considers in Determining the Drug Equivalency for Analogues and Controlled Substances Not Referenced in §2D1.1 Should Be Revisited

Defenders encourage the Commission to review the factors listed in §2D1.1, comment. (n.6), especially given the ever-changing nature of synthetic drugs and the need for courts to have to continue applying that commentary. The commentary in Note 6 directs the court to consider “to the extent practicable” in determining the “most closely related controlled substance” referenced in §2D1.1 the following factors:

- (A) Whether the controlled substance not referenced in this guideline has a chemical structure that is substantially similar to a controlled substance referenced in this guideline.
- (B) Whether the controlled substance not referenced in this guideline has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance referenced in this guideline.

⁵⁴ Barry K. Logan et al., *Identification of Synthetic Cannabinoids in Herbal Incense Blends in the United States*, 57 J. Forensic Sci. 1168 (2012) (“The recipes usually call for the addition of 1 g of active ingredient to 50 g of leaf material for a final concentration of 20 mg per gram of substrate.”).

⁵⁵ United Nations Office on Drugs and Crime, *Synthetic Cannabinoids in Herbal Products* 4 (2011), https://www.unodc.org/documents/scientific/Synthetic_Cannabinoids.pdf.

(C) Whether a lesser or greater quantity of the controlled substance not referenced in this guideline is needed to produce a substantially similar effect on the central nervous system as a controlled substance referenced in this guideline.

USSG §2D1.1, comment. (n.6).

Our experience with application of this guideline shows four key problems. First, the current standard creates disparity because the term “substantially similar” has no standard or accepted definition in the fields of chemistry or toxicology/pharmacology.⁵⁶ The lack of a standard definition results in inconsistent application of the guidelines and disparate sentences for the same drug.⁵⁷

Second, as Judge Thompson pointed out over six years ago: “[a]fter there has been a determination of the listed drug most closely related to the unlisted drug, the Sentencing Guidelines do not provide a method to adjust the base-offense level for any potency difference remaining between the listed drug and the unlisted drug.”⁵⁸ The failure to do so has been a problem in many cases. For example, in methylone cases, MDMA is often found to be the most

⁵⁶ See *United States v. Ketchen*, 2015 WL 3649486, at *12 (D. Me. June 11, 2015) (noting forensic chemist’s comment that the “substantially similar” standard set forth in § 802(32)(A) “has no quantifiable meaning” and results in opinions based on “little more than subjective feelings about the appearance of two-dimensional diagrams”); Transcript of Motions Hearing, at 27–28, 34 *United States v. Ilan Fedida*, 8:12-mj-1457TGW (M.D. Fla. Dec. 6, 2012) (forensic chemist Lindsay Reinhold discussing lack of scientific method to determine if a drug is “substantially similar” and how it is a matter of each chemist’s opinion); *id.* at 82 (chemist Terry Stouch describing the phrase “substantially similar” as “essentially nonsense” in the field of chemistry).

⁵⁷ See, e.g., *United States v. Marte*, 586 F. App’x 574, 575 (11th Cir. 2014) (relying in DEA pharmacologist’s testimony that “methylone is half as potent as MDMA,” the district court properly used a 1:250 ratio); *United States v. Chin Chong*, 2014 WL 4773978 (E.D. N.Y. Sept. 22, 2014) (1:200 ratio for methylone); *United States v. Breton*, 2016 WL 7436602, at *2 (2d Cir. 2016) (1:500 ratio for methylone); *United States v. Nicholas Pangourelis*, No. 8:14-CR-303-T-23EAJ (M.D. Fla. Feb. 19, 2015) (1:500 ratio for methylone); Government’s Sentencing Memorandum, at 3, *United States v. Gattis*, No. 3:12-cr-00074-01-RRB (D. Ak. Nov. 26, 2013) (parties agreed that methylone was most closely related to methcathinone and used 1:380 gram ratio); *United States v. Holmes*, 2016 WL 1611579 (D. Haw. 2016) (rejecting government and probation’s position that ethylone is most closely related to MDEA, which would have resulted in a 1:500 ratio, and instead finding that ethylone is most closely related to methcathinone with a 1:380); *United States v. Malespin*, 15-CR20350-CMA (S.D. Fla. Oct. 27, 2015) (adopting 1:250 ratio for ethylone based on defense expert testimony that chemical structure of ethylone was closer in similarity to methcathinone); *United States v. Brey*, 627 F. App’x 775, 778 (11th Cir. 2015) (finding that ethylone was most closely related to MDEA and using 1:500 ratio).

⁵⁸ *United States v. Rose*, 722 F. Supp. 2d 1286, 1289 (N.D. Ala. 2010). See also *United States v. Chowdhury*, 639 F.3d 583, 568, n.2 (2d Cir. 2011) (relative potency of drugs is appropriately considered under 18 U.S.C. § 3553(a)).

closely related substance, but the evidence is clear that methylone is half-as-potent. Yet, the guidelines provide no mechanism to adjust the guideline range according to potency. As a result, some prosecutors and courts insist on a 1:500 ratio for methylone while others adopt a 1:250 ratio.

Third, the language of the guideline that requires the court to consider the listed factors “to the extent practicable” also generates disparity and outcomes that are not as evidence-based as possible. The problem with this language is apparent in the Eleventh Circuit’s decision in *United States v. Brey*, 627 F. App’x 775 (11th Cir. 2015). The panel approved a district court’s decision to adopt a 1:500 ratio for ethylone even though the government presented no evidence about the third factor listed in the commentary—quantity “needed to produce a substantially similar effect on the central nervous system”:

But Brey’s argument that the lack of evidence of potency is fatal to government’s position—and the district court’s ultimate conclusion—is not supported by the commentary to § 2D1.1. Application Note 6 does not impose an absolute duty on the government to produce evidence about all three factors; rather, it requires only that the district court consider the three factors “to the extent practicable.” U.S.S.G. § 2D1.1 cmt. n. 6 (emphasis added). The guidelines thus recognize “that, in some circumstances, sentencing courts will be unable to match substances under each of the factors.” *United States v. Chowdhury*, 639 F.3d 583, 586 (2d Cir. 2011). In short, the absence of specific and reliable evidence as to one of the factors, such as potency, does not preclude a court from making a determination as to the most closely related controlled substance under Application Note 6. *See id.* (holding that the district court did not clearly err in substituting MDMA for the substance in question despite the “absence of a substance with a substantially similar chemical structure, or reliable information regarding the relative potency of the two substances” (internal citations omitted)).

Brey, 627 F. App’x at 780–81.

Fourth, the third factor regarding “the quantity of the controlled substance not referenced in [the] guideline” that is “needed to produce a substantially similar effect on the central nervous system as a controlled substance referenced in the guideline” has presented interpretive difficulties and resulted in unduly high ratios. The Eighth Circuit’s decision in *United States v. Ramos*, 814 F.3d 910 (8th Cir. 2016), shows one of the problems with the third factor.⁵⁹ In *Ramos*, a panel majority upheld the district court’s decision that THC was the most closely related substance to various synthetic cannabinoids, including XLR-11, and therefore a 1:167 ratio was appropriate. The court rejected the argument that the district court should have examined the effects of

⁵⁹ Other interpretive problems with note 6 are related to §2D1.1’s inconsistent and confusing approach to how dosage, mixtures, and purities factor into the sentencing guidelines. *See* Discussion I, *supra*.

synthetic cannabinoid potpourri rather than pure synthetic cannabinoids alone, reasoning that synthetic cannabinoid potpourri is not listed as a controlled substance. *Id.* at 919. Judge Bright, however, dissented from the court’s application of factor C in §2D1.1, comment. n.6:

The majority, however, contends the sentencing judge correctly applied Factor C when it considered only the effect of the synthetic cannabinoids. The majority concludes the plant material should not be considered in conjunction with “synthetic cannabinoids, such as XLR–11, [because synthetic cannabinoids] are listed in Schedule I . . . [not] ‘synthetic cannabinoid potpourri.’” To support this interpretation, the majority relies upon three words in Factor C—“the controlled substance.”

[B]y limiting its interpretation to three words in Factor C, the majority fails to take into account “the language and design of the [Guidelines] as a whole.” In the context of Factor C, Application Note 6 plainly calls for the consideration of plant material when assessing which THC-based controlled substance is “most closely related” to a THC analogue. This is required specifically because THC is treated differently than other controlled substances in the Guidelines—namely THC is both a controlled substance and the psychoactive ingredient in other controlled substances. Consequently, the majority’s analysis leads to the unreasonable result that the “most closely related controlled substance” can never be marijuana, hashish, or hashish oil because it is improper to consider the presence of plant material when analyzing THC analogues. In my view, the majority’s conclusion is contrary to the plain language of Application Note 6 and the treatment of THC in Guidelines.

Id. at 923–24 (Bright, J., dissenting) (citations omitted).

To resolve the confusion, the Commission should clarify that it seeks to similarly punish crimes involving similar dosage amounts of drugs of similar harmfulness.

B. To Help Ensure That the Sentences Imposed for Drugs Not Referenced in §2D1.1 Are Similar to Drugs That Have Similar Harms, the Commission Should Consider Amending §2D1.1, comment. n.6

First, the consideration of “chemical structure,” per se, should be eliminated. Litigation over the “chemical structure” of unreferenced drugs has been one of the causes of the “extensive hearings” noted in the request for comment. Moreover, testimony about chemical structure, which can be quite technical, is only indirectly relevant to the considerations that should be the focus of inquiry—the direct harms of a drug, how those harms compare with other drugs, and any differences in the amount of the unlisted substance at issue contained in a typical dose. There is, of course, no question that chemical differences affect the pharmacological properties and adverse health effects of various substances. But what is needed is explicit consideration of those properties and effects. Chemical structure, per se, is largely a highly technical “red herring.”

Second, we believe that subsection B's focus on the unlisted substance's "stimulant, depressant, or hallucinogenic effect on the central nervous system" is misplaced. Psychoactive substances have complex and varying effects on the central nervous system, differentially affecting various brain areas, neuron types, and other systems. They can mimic neurotransmitters, inhibit their re-uptake, and stimulate arousal systems or inhibitory systems. The relation of these neurological effects to the psycho-pharmacology of drugs is enormously complex and an active area of research. But as with chemical structure, a focus on the effect of a drug on the central nervous system runs the risk of having the court consider highly technical matters of only indirect relevance to a drug's direct harms.

The terms "stimulant, depressant, or hallucinogenic" refer less to a drug's "effect on the central nervous system" than to its behavioral manifestations and to the subjective experience of taking the drug. The pharmacological literature, and especially user reports, displays a keen interest in comparing these manifestations and experiences, which can vary among users even for the same drug. Defenders do not believe it is helpful when determining proper sentences for the Commission or the courts to consider evidence of the type of experience users tend to have. How significant is it that a particular synthetic cathinone tends to produce "speedier" stimulant experiences like amphetamines, compared to "trippier" or "headier" more "hallucinogenic" experiences like MDMA (which has also been described as "empathic" or even "entheogenic")?

Defenders believe that it would be better, and more consistent with the overall structure of the guidelines, for the court to focus on evidence of the direct harms of different drugs. Chemical structure and central nervous system effects certainly affect such harms, but the evidence most relevant for sentencing is both different and, in many respects, more accessible and understandable. Pharmacological and public health research and data are available for many drugs on factors such as addiction potential, toxicology (both neurotoxicity and other organ damage), overdose risk, and other measures of direct harm. The risk aspect of such data raises an important point. It is not mere examples or anecdotes of negative or even fatal drug exposures that are needed; rather some analysis of the likelihood of such outcomes is needed, given the overall number of uses, as well as the roles of contributory causes not inherent in the drug itself.

In short, Defenders believe both the Guidelines and courts should refocus on evidence of these medical and public health harms, and on identifying which of the listed controlled substances are most similar to the unlisted substance in terms of these harms. The analysis should focus on what the medical and public data say about addiction potential, risk of emergency room visits, overdose deaths, etc., rather than "chemical structure" or "central nervous system" effects.

Third, Defenders agree with the gist of the current third prong to the extent it reflects the Commission's recognition of the importance of dosage amount, which we believe should be applied more generally and consistently throughout the drug guidelines. However, we recommend refining and clarifying for courts how this consideration is relevant to the overall

rationale of drug sentencing. Simply by explaining, in commentary or elsewhere, how drug type and quantity (which of course raise issues of dosage amount and purity) relate to sentencing purposes would not only improve sentencing fact-finding in the courts, but also may generate improved feedback to the Commission on how the guidelines' approach works and when it encounters difficulty.

We believe it could significantly clarify both sentencing and sentencing policy-making in drug trafficking cases if the Commission clearly stated, and judges understood, that the aim of considering drug type and quantity is to impose, to the extent practicable, similar sentences on similar effective amounts of drugs that result in similar direct harms. Obviously, this general principle needs to be elaborated, taking into account purities, typical effective dosage amounts, and focusing on the relevant harms, as described earlier. We encourage the Commission to use this multi-year project to do so and offer our help in any way that may be useful. Clearly, this principle also has implications for the drug guidelines beyond the drugs at issue here. Unfortunately, rationalizing the guidelines entirely may not be possible so long as statutory constraints limit the Commission's options. But we urge the Commission to go as far as possible, like the first Commission did when it re-evaluated the best approach to sentencing offenses involving LSD.

C. If the Commission Does Not Revise §2D1.1, comment. (n.6), It Should Include an Invited Departure for Cases Where the Drug Is Less Potent than the One to Which It Is Deemed "Most Closely Related"

If the Commission chooses not to amend §2D1.1, comment. (n.6) to directly account for the potency of a drug, Defenders request that it include within the guidelines an invited downward departure for cases where the drug is less potent than the drug the court has determined to be the most "closely related controlled substance." For example, in *United States v. Rose*, 722 F. Supp. 2d 1286 (M.D. Ala. 2010), both the government and the court believed it appropriate to consider a variance where the drug at issue (BZP) was less potent than the most "closely related" substance. As the court noted: "[a]fter there has been a determination of the listed drug most closely related to the unlisted drug, the Sentencing Guidelines do not provide a method to adjust the base-offense level for any potency difference remaining between the listed drug and the unlisted drug. This potency adjustment, if warranted, may therefore be appropriately addressed as a variance."⁶⁰ Including an invited departure in §2D1.1, comment. (n.6) would be consistent

⁶⁰ *Rose*, 722 F. Supp. 2d at 1289. See also *United States v. Major*, 801 F. Supp. 2d 511, 514 (E.D. Va. 2011) (noting that some courts have found it sensible to grant a variance where the drug not referenced in the guidelines is "significantly less potent" than the "most closely related" substance); *United States v. Qayyem*, 2012 WL 92287, at *7 (S.D.N.Y. 2012); *United States v. Chowdhury*, 639 F.3d 583, 586, n.2 (2d Cir. 2011) (acknowledging that the relative potency of two narcotics is appropriately considered under 18 U.S.C. § 3553(a)).

with the decision the Commission finally made in determining the marijuana equivalency for BZP, i.e., that BZP is similar to amphetamine, but “only one-tenth to one-twentieth as potent.”⁶¹ Because it is impossible for the Commission to constantly track and add equivalencies for analogue drugs, Defenders believe that an invited departure will help promote greater uniformity in sentencing because many of these drugs have been deemed less potent than the drugs to which they have been deemed “most closely related.”⁶²

IV. General Comments on Nature of Offenses Involving MDMA and Specific Synthetic Drugs

The Commission seeks comment on a number of topics related to offenses involving synthetic cathinones (MDPV, methylone, and mephedrone) and synthetic cannabinoids (JWH-018 and AM-2201); conduct involved in such offenses; nature and seriousness of the harms posed by such offenses; how these offenses and individuals convicted of them compare to other drug offenses and individuals convicted; how these substances are manufactured, distributed, possessed and used; the characteristics of individuals involved in these activities; the harms posed by these activities; and which substance referenced in §2D1.1 is most closely related to the synthetic drugs being considered in the study. While we remain hopeful that the Commission will consider more scientific data on the direct harms of these drugs, here we take the opportunity to respond to the Commission’s broader approach.

A. General Nature of Offenses and Persons Involved in Trafficking Synthetic Cathinones and Cannabinoids

A random sample of nationwide federal prosecutions of persons involved in trafficking synthetic cathinones and cannabinoids reveals a wide variety of cases—some involving higher level traffickers and others involving couriers and low-level street dealers. The conduct involved in these offenses is not more serious than that involved in other drug trafficking offenses. Few cases

⁶¹ USSG App. C, Amend. 762 (Nov. 1, 2012).

⁶² See, e.g., *United States v. McGuire*, No. 8:13-CR-421-T-35TGW (M.D. Fla. April 16, 2015) (J. Scriven) (using a 1:200 marijuana-methylone ratio after finding that methylone is only 50% potent as MDMA and that MDMA should have lower ratio); *United States v. Sakairi*, No. 6:14-CR-00108-GKS-TBS (M.D. Fla. Dec. 16, 2014) (J. Sharp) (same); Stipulation, *United States v. Konarksi et al.*, No. 2:13-CR-00071-NBF (W.D. Pa. Aug. 19, 2014) (parties agree that “appropriate conversion ratio from Methylone to Marijuana is: 1 gram of Methylone to 250 grams of Marijuana”); *United States v. Poole*, No. 4:13-cr-00066-CVE (N.D. Ok. Aug. 26, 2013) (J. Eagan) (granted variance to 1:250 ratio for methylone); *United States v. Meredith*, No. 8:14-CR-505-T-35AEP (M.D. Fla. Mar. 7, 2016) (J. Scriven) (finding ethylone to be substantially similar to methylone and granting a variance for a 1:200 ratio).

involve aggravating conduct, such as the use of weapons, bodily injury, or sale at protected locations.⁶³

Many people who sell and use these drugs believe they are legal, given that they can be purchased from businesses and on-line rather than in a back alley or some secret spot like other drugs.⁶⁴ Many Defender clients have been people who suffered from addiction and sold the drugs to support their own habits rather than for personal gain. For example, in one case, a 21-year-old male from a single-parent family who liked to get high was introduced to “Molly” – methylone. He and his co-defendant obtained their Molly, which was marketed as bath salts, from China. Because state law did not make the drug unlawful, they naively thought it would be legal for them to buy it and then sell at parties to their friends.

Traffickers who import the drugs typically do so from China via the internet and are often caught when postal inspectors intercept the package or confidential informants purchase the drugs. In some cases, the drugs are transported across the border.⁶⁵ Individuals who are above street-level dealers often are involved in businesses such as gas stations, convenience stores, and tobacco shops that sell the drugs behind the scenes, without using a cash register or providing receipts, or over the internet. Some obtain the chemicals from China and then manufacture synthetic marijuana (spice/K2) by spraying the chemicals on plant materials, like marshmallow leaves. Both synthetic marijuana and bath salts are packaged and often labeled not for human consumption. Some of the higher level individuals have forfeited a large amount of money even after being sentenced to long prison terms. One case involved a Chinese man sentenced to 50 months imprisonment who also forfeited \$1.5 million.⁶⁶

⁶³ See generally USSC, *Interactive Sourcebook*, tbl. 33, FY2012-2015 (the Commission’s dataset does not break down the types of synthetic drugs, but other than MDMA, all the drugs at issue here fall within the “other” category).

⁶⁴ See, e.g., Transcript of Deposition Testimony of Louis Schmidt (DEA Special Agent), at 57, *United States v. Chin Chong*, No. 1:13-CR-00570-JBW (E.D.N.Y. Jan. 2, 2014).

⁶⁵ In one case, the defendant drove cocaine to a remote part of the Canadian border to exchange it for ecstasy that was being backpacked to the United States from Canada.

⁶⁶ U.S. Immigration & Customs Enforcement, News Releases: *Chinese Chemical Engineer Sentenced for Synthetic Drugs* (Apr. 29, 2016), <https://www.ice.gov/news/releases/chinese-chemical-engineer-sentenced-synthetic-drugs> Chinese chemical engineer sentenced for synthetic drugs.

B. MDMA and Specific Synthetic Drugs

1. The Current 1:500 MDMA-to-Marihuana Ratio Seriously Overstates the Harms Associated with MDMA

The Commission should change the ratio for MDMA to better reflect advances in scientific knowledge since 2001.⁶⁷ In 2001, in response to a Congressional directive to increase the sentences for MDMA, the Commission changed the marijuana equivalency ratio from 1:35 grams to 1:500 grams – 2.5 times the ratio for cocaine.⁶⁸ The Commission gave three key reasons to justify this increase: (1) cocaine is only a stimulant, while MDMA is both a stimulant and hallucinogen;⁶⁹ (2) MDMA is “neurotoxic” and has “unique pharmacological and physiological harms;”⁷⁰ and (3) MDMA is more aggressively marketed to youth than cocaine.⁷¹ The reasons for such a dramatic increase in the MDMA ratio are unsupported by empirical evidence. Substantial evidence shows that MDMA is less harmful than cocaine and is not properly characterized as a hallucinogen in all instances.⁷² A well-designed study also has shown that MDMA is not appropriately characterized as neurotoxic.⁷³ And the most recent data on teen use of illicit drugs shows a decline in the use and availability of MDMA.⁷⁴ Of twelfth graders,

⁶⁷ We previously have provided information on why the Commission should revisit the MDMA ratio. *See, e.g.,* Letter from Marjorie Meyers, Chair, Federal Defender Sentencing Guidelines Committee, to the Honorable Patti B. Saris, Chair, U.S. Sentencing Comm’n, at 8–13 (July 15, 2013).

⁶⁸ USSG App. C, Amend. 621 (Nov. 1, 2001).

⁶⁹ *Id.*

⁷⁰ USSC, *Report to the Congress: MDMA Drug Offenses* 5 (2001).

⁷¹ *Id.*

⁷² *United States v. McCarthy*, 2011 WL 1991146, at *3 (S.D.N.Y. 2011). *See also* European Monitoring Centre for Drugs and Drug Addiction, *Methylenedioxymethamphetamine (MDMA or “Ecstasy”) Drug Profile* (2017) (MDMA has “a weak hallucinogenic property more accurately described as increased sensory awareness”), <http://www.emcdda.europa.eu/publications/drug-profiles/mdma>.

⁷³ *See generally* J. Halpern et al., *Residual Neuropsychological Effects of Illicit 3,4-Methylenedioxymethamphetamine (MDMA) in Individuals with Minimal Exposure to Other Drugs*, 75 *Drug & Alcohol Dependence* 135 (2004).

⁷⁴ Lloyd Johnston et al., Univ. of Michigan Institute for Social Research, *Monitoring the Future National Survey Results on Drug Use: 2016 Overview, Key Findings on Adolescent Drug Use* 36 (2017), <http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2016.pdf>.

2.7% used MDMA and 2.3% used cocaine.⁷⁵ Also relevant to the Commission’s consideration of MDMA is that MDMA-assisted psychotherapy has shown to be an effective treatment for people suffering from Post-Traumatic Stress Disorder.⁷⁶

As the Commission is aware, the court in *United States v. McCarthy*, ruled that the Commission overstated the ratio for MDMA.⁷⁷ The court reached that conclusion after an extensive hearing with four experts.⁷⁸ Among the experts was Dr. Valerie Curran—a psychopharmacologist. Dr. Curran testified about studies of MDMA that had been done after the Commission’s 2001 decision to adopt a 500:1 MDMA-to-marijuana ratio, including brain imaging studies that had not been done before.⁷⁹ Dr. Curran also explained how the 2001 studies relied upon by the Commission “were not applicable” because “it was not valid to generalize from those incredibly toxic doses in animals to humans who use 100 milligrams one or twice month.”⁸⁰ The drawback of animal studies was “giving these incredibly high toxic doses to animals twice a day for 4 days and injected, which you can’t then generalize to a human who uses a pill one or twice a month.”⁸¹ Part of the problem was that “[i]njecting a drug has different effects from taking it through the gut and into the brain” and “humans metabolize MDMA” differently than “rats and monkeys,” “which makes generalization not possible directly from one to the other.”⁸² Dr.

⁷⁵ National Institute on Drug Abuse, *Teen Drug Use: Monitoring the Future 2016*, at 6 (2016), <https://www.drugabuse.gov/related-topics/trends-statistics/infographics/monitoring-future-2016-survey-results>.

⁷⁶ See generally *Treating PTSD with MDMA-Assisted Psychotherapy*, <http://www.mdmaptsd.org/news.html>; Ben Sessa & David Nutt, *Making a Medicine Out of MDMA*, 206 *British J. Psychiatry* 4–6 (2015).

⁷⁷ *United States v. McCarthy*, 2011 WL 1991146 (S.D.N.Y. 2011).

⁷⁸ Appendix A is a transcript of the hearing conducted in *McCarthy* on December 6 and 7, 2010 (hereinafter *McCarthy Hearing Transcript*). Witnesses were Dr. Helen Curran – a psychopharmacologist; Dr. John Halpern – a psychiatrist; Dr. Andrew Parrott – a psychologist; and Dr. Glen Hanson – a pharmacologist and toxicologist.

⁷⁹ *McCarthy Hearing Transcript*, at 10.

⁸⁰ *Id.* at 13. See also *id.* at 22–28 (discussing specific studies); *id.* at 34–41 (discussing specific problems with the Commission’s 2001 report on the harms of MDMA)

⁸¹ *Id.* at 16.

⁸² *Id.*

Curran also discussed in detail what kinds of studies are most reliable.⁸³ She concluded that MDMA “is less harmful than either ketamine or marijuana.”⁸⁴

Dr. Halpern, a psychiatrist with expertise in hallucinogens, testified that the Commission’s 2001 report is “out of date and excessively harsh in its conclusions.”⁸⁵ Research conducted after 2001 used different technology than what was used in the past, such as brain imaging, and controlled for mental illness and actual MDMA use in human rather than animal studies.⁸⁶ The more current research shows for the majority of people who use MDMA illegally, “the harms appear to be quite modest and time-limited.”⁸⁷ For example, Dr. Halpern’s study of MDMA users compared to non-users found no statistically significant different results in cognitive testing except for heavy MDMA users.⁸⁸ In addition, MDMA resulted in fewer emergency room visits than cocaine and is not neurotoxic.⁸⁹ Dr. Halpern’s testimony describes in detail other inaccuracies in the 2001 Commission study⁹⁰ and explained that MDMA does not produce the same hallucinogenic effects as drugs like LSD or mescaline.⁹¹

While suggesting that more recent studies confirmed the “psychobiological deficits associated with MDMA that were known in 2001,”⁹² the government’s witness, Dr. Parrott, agreed with Dr. Halpern that the hallucinogenic properties of MDMA “are really quite mild” and indicated he would “characterize MDMA as a stimulant and energetic stressor rather than hallucinogen.”⁹³ Dr. Parrott also expressed his view that cocaine is “far more addictive than MDMA” and the problems associated with MDMA “won’t be as severe as many of the problems of cocaine.”⁹⁴ A

⁸³ *Id.* at 22–23.

⁸⁴ *Id.* at 13.

⁸⁵ *Id.* at 115.

⁸⁶ *Id.* at 116–120.

⁸⁷ *Id.* at 122.

⁸⁸ *Id.* at 124.

⁸⁹ *Id.* at 126, 129.

⁹⁰ *Id.* at 131–134.

⁹¹ *Id.* at 164.

⁹² *Id.* at 178–79.

⁹³ *Id.* at 289–90.

⁹⁴ *Id.* at 291–92.

paper Dr. Parrott published about drug harms ranked cocaine as second and MDMA as fifth.⁹⁵ Dr. Hanson also agreed that MDMA is less addictive than cocaine, but believed they shared “certain harms.”⁹⁶ Nonetheless, he testified that “unlike cocaine users even heavy users generally decline in their use of MDMA.”⁹⁷

As a result of this testimony, the court in *McCarthy* adopted a 1:200 MDMA-to-marihuana equivalency. Other courts have followed *McCarthy* and recognized problems with the MDMA-to-marihuana ratio.⁹⁸

The problems with the MDMA ratio were more recently reaffirmed in other cases with extensive evidentiary hearings.⁹⁹ For example, in deciding that methcathinone is the most closely related drug to eythylone, Judge Susan Mollway in the District of Hawaii, relied upon Dr. Halpern’s testimony:

[Dr. Halpern] criticized several marijuana ratios in the Drug Equivalency Tables as incompatible with today’s scientific data. He pointed, for example, to cocaine, which has a 1:200 ratio, and questioned why drugs like MDMA and MDEA had 1:500 ratios when they were less harmful than cocaine. He not only described a study he had conducted involving MDMA users, he also noted that cocaine use results in more medical emergencies, more deaths, more violence, and more abuse than MDMA or MDEA use.

United States v. Holmes, 2016 WL 1611579, at *7 (D. Haw. Apr. 22, 2016).

⁹⁵ *Id.* at 293.

⁹⁶ *Id.* at 337, 340.

⁹⁷ *Id.* at 369.

⁹⁸ See, e.g., *United States v. Qayyem*, 2012 WL 92287 (S.D.N.Y. 2012); Transcript of Proceedings at 9, *United States v. Dafang*, 1:14-cr-00722-JMS (D. Haw. Feb. 2, 2015); *United States v. Thompson*, 2012 WL 1884661 (S.D. Ill. May 23, 2012) (“considerable uncertainty exists as to the science and policies underlying the marijuana-to-MDMA ratio”); *United States v. Kamper*, 860 F. Supp. 2d 596, 602 n.7, 603 n.9 (E.D. Tenn. 2012) (“More recent studies . . . have largely discredited the earlier studies, particularly as related to [the Commission’s assertion that MDMA is] neurotoxic[,]” and the claim that MDMA is a hallucinogen “is without factual support and largely irrelevant”); Transcript of Sentencing 2–4, 6–8, 14–16, *United States v. Phan*, No. CR10-27 (W.D. Wash. Mar. 3, 2011) (recognizing that the MDMA ratio is flawed).

⁹⁹ See, e.g., *United States v. Chin Chong*, 2014 WL 4773978, at *15 (E.D.N.Y. 2014). See also Transcript of Telephonic Deposition of Dr. John Halpern, *United States v. Chin Chong*, No. 1:13-CR-00570-JBW (E.D.N.Y. Aug. 22, 2014) (attached as Appendix B); Declaration of Dr. Gregory Dudley, *Chin Chong* (July 24, 2014) (attached as Appendix C).

Another expert, Dr. Charles Grob—a psychiatrist specializing in hallucinogens—presented testimony in *United States v. Chin Chong*, which reaffirmed Judge Pauley’s ruling in *McCarthy* that “MDMA causes significantly less risk of injury to users than cocaine, and consequently that its illicit use should be subject to a lesser degree of punishment as per sentencing guidelines, compared to cocaine.”¹⁰⁰ Among other things, Dr. Grob testified that cocaine has a “high addiction potential, whereas MDMA does not cause physiological addiction;” that [c]ocaine is far more likely to precipitate episodes of violence and agitation than MDMA; and that “the fears of MDMA induced brain damage have been grossly overstated.”¹⁰¹

Commission data also shows that the guidelines for MDMA are too high. Seventy-six percent of individuals sentenced for ecstasy between 2013 and 2015 received a below range sentence (41.6% government sponsored and 34.8% non-government sponsored).¹⁰²

2. The Harms Associated with Synthetic Cathinones and Cannabinoids Are Often Overstated

The nature and seriousness of the harms associated with synthetic drugs are often overstated. While some users of various synthetic drugs may experience severe health and psychological effects, these effects are not common. A psychiatrist, Dr. Charles Grob, experienced with substance abuse notes that he is aware of “only a very small number of patients who had presented with methylone or other synthetic cathinone abuse.”¹⁰³ For Dr. Grob’s assessment of the limited adverse effects of synthetic cathinones and how methylone is less problematic than mephedrone and MDPV, see Appendix D, at 3–5. And methylone, compared to “the prototype psychostimulant cocaine . . . is much milder, less likely to be habit forming or addictive, far less likely to be associated with violent behavior and implicated in far fewer fatalities.”¹⁰⁴ MDPV, however, has “far greater similarities to cocaine’s effects on the momoamine dopamine than does

¹⁰⁰ Declaration of Charles Grob, *Chin Chong* (attached as Appendix D).

¹⁰¹ *Id.* at 5–6.

¹⁰² USSC, *FY2013-2015 Monitoring Dataset*. See also Transcript of Resentencing, at 63–64, *United States v. Head*, No. 1:11-CR-3 (E.D. Tenn. May 21, 2015) (granting a downward variance, in part, to avoid disparity in application of the MDMA guideline because most judges did not impose sentences within the guideline range).

¹⁰³ Declaration of Charles S. Grob, M.D., at 5, *United States v. Thannavongsa*, 2:13-CR-00255-JAD-GWF (D. Nev. July 16, 2014) (attached as Appendix E).

¹⁰⁴ *Id.* at 5.

methylone.”¹⁰⁵ And “mephedrone induced much higher levels of drug self-administration than did methylone.”¹⁰⁶

C. Most Closely Related Substances

The Commission requests comment on “[w]hich of the controlled substances currently referenced in §2D1.1 should be identified as the ‘most closely related’ controlled substance to any of the synthetic cathinones and synthetic cannabinoids included in the Commission’s study” and the extent to which the synthetics “differ from its ‘most closely related controlled substance.’” The research on many synthetic drugs is insufficient for the Commission to precisely determine the “most closely related” substance and then develop a rational drug equivalency.¹⁰⁷ We understand, however, that the Commission intends to propose amendments that will identify equivalencies for these substances. To avoid overstating the harms associated with these drugs, as happened with crack cocaine,¹⁰⁸ the Commission should approach the issue like a court would do in applying the rule of lenity—resolve the debate about the appropriate controlled substance in favor of the defense. The rule of lenity approach will help ensure that individuals convicted of offenses involving these drugs are not sentenced to terms of imprisonment far in excess of what would be reasonable and proportional.

1. Synthetic Cathinones

a. MDPV

Evidence from the Drug Enforcement Administration and other sources supports the conclusion that MDPV is a stimulant related to pyrovalerone—a Schedule V substance.¹⁰⁹ It also reportedly has effects “similar to methylphenidate at low doses and cocaine at high doses.”¹¹⁰ Accordingly,

¹⁰⁵ *Id.* at 3.

¹⁰⁶ *Id.*

¹⁰⁷ See Lisa Sacco & Kristin Finklea, Congressional Research Service, *Synthetic Drugs: Overview and Issues for Congress* 1 (2016) (“Due to the lack of research on many of these synthetics and their various analogues, the full scope of their effects and potential dangers is still not well known”).

¹⁰⁸ See USSC, *Cocaine and Federal Sentencing Policy* 21–30 (2002).

¹⁰⁹ See Barry Logan, *SOFT Designer Drug Committee Monographs, Emerging Designer Drug Monography: MDPV* (Sept. 13, 2013); Joshua Yohannan & Joseph Bozenko, *The Characterization of 3,4-Methylenedioxypropylpyrovalerone (MDPV)*, 7 *Microgram Journal* 12–15 (Mar. 2010), https://www.dea.gov/pr/microgram-journals/2010/mj7-1_12-15.pdf; 21 Fed. Reg. 1308.15 (May 12, 2016).

¹¹⁰ Logan, *supra* note 109, at 2.

the evidence supports treating a Schedule V substance as the most closely related controlled substance to MDPV, which would result in a marijuana equivalency ratio of 1 unit of MDPV-to-.00625gm of marijuana. If the Commission, however, chooses not to apply the rule of lenity in determining the most closely related controlled substance, then it should compare MDPV to methylphenidate, which has a ratio of 1:100.

b. Methylone

The limited research available shows that methylone does not deplete serotonin like MDMA.¹¹¹ Dr. Gregory Dudley has opined that “methylone is more similar in chemical structure to cathinone than it is to MDMA.”¹¹² After an extensive review of available research, Dr. DeCaprio stated that “[t]he bulk of pharmacological evidence . . . supports a conclusion that methylone is, on average, 5-fold less potent than MDMA for a variety of endpoints relevant to the psychoactive effects of this class of drugs of abuse.”¹¹³ Accordingly, even if the Commission were to conclude that MDMA is the most closely related substance to methylone, the marijuana equivalency ratio should account for the lesser potency.

c. Mephedrone

Defenders have not been able to collect sufficient information to comment on mephedrone, particularly since the factors in Note 6 have not been litigated to the same degree as other synthetic drugs. In addition, most of the literature combines all synthetic cathinones into a single entity even though it is clear that each substance is different. Defenders strongly urge the Commission to remove this substance from its multi-year study.

2. Synthetic Cannabinoids

DEA and independent experts have agreed that synthetic cannabinoids do not have a chemical structure similar to marijuana or THC.¹¹⁴ Some disagree, however, about whether the effects of

¹¹¹ University of Wisconsin School of Public Health, News and Events: *Study Suggests Possible Therapeutic Use for “Bath Salt” Designer Drugs*, (describing Baumann et al., *The Designer Methcathinone Analogs, Mephedrone and Methylone, are Substrates for Monoamine Transporters in Brain Tissue*, 37 *Neuropsychopharmacology* 1192 (2012), <http://www.med.wisc.edu/news-events/study-suggests-possible-use-for-bath-salt-designer-drugs/36980>).

¹¹² Declaration of Dr. Gregory Dudley, (Tallahassee, Florida, July 24, 2014) (attached as Appendix F).

¹¹³ Declaration of Dr. Anthony Decaprio, at 9, *Chin Chong* (July 24, 2014) (attached as Appendix G).

¹¹⁴ USSG §2D1.1, comment. (n.(6)(A)). See, e.g., *United States v. Tebbetts*, No. 5:12-CV-567 (N.D.N.Y. May 14, 2014); *Hossain*, 2016 WL 70583, at *2; Drug Enforcement Administration, Office of Diversion Control, *JWH-018, 1-Pentyl-3-(1-naphthoyl)indole [Synthetic Cannabinoid in Herbal Products]*, at 1 (JWH-018 is not categorized as a THC substance, and is not similar in chemical structure to other

synthetic cannabinoids on the central nervous system are similar to THC.¹¹⁵ Experts also disagree about the significance of animal studies. A government expert typically cites drug discrimination studies to support the claim that THC is the most closely related substance. In such studies, “animals could not differentiate” between some of the synthetic cannabinoids and THC.¹¹⁶ Other experts, explaining the flaws in the studies relied upon by the government, conclude that marijuana is the most closely related substance.¹¹⁷ Another issue of debate is whether a mixture or substance containing some portion of synthetic cannabinoids is appropriately compared to pure THC or marijuana, which is a mixture or substance containing THC.¹¹⁸

Defenders strongly encourage the Commission to treat a mixture of substance containing synthetic cannabinoids the same way as a mixture of substance containing THC. The Drug Equivalency Table¹¹⁹ lists 4 ratios for 5 different forms of Schedule I Marihuana:

1 gm of Marihuana/Cannabis, granulated, powdered, etc. =	1 gm of marihuana
1 gm of Hashish Oil =	50 gm of marihuana
1 gm of Cannabis Resin or Hashish =	5 gm of marihuana
1 gm of Tetrahydrocannabinol, Organic =	167 gm of marihuana
1 gm of Tetrahydrocannabinol, Synthetic =	167 gm of marihuana

substances controlled under the CSA) (hereinafter DEA, *JWH-018*), https://www.deadiversion.usdoj.gov/drug_chem_info/spice/spice_jwh018.pdf.

¹¹⁵ USSG §2D1.1, comment. (n.6(B)). See *Hossain*, 2016 WL 70583, at *3 (describing independent expert’s testimony that XLR-11 binds more strongly to the CB2 receptor than the CB1 receptor, which was contrary to DEA expert’s testimony); DEA, *JWH-018*, at 1 (relying on animal tests that suggests *JWH-018* is “likely to have THC-like psychoactive effects in humans”).

¹¹⁶ See, e.g., *Hossain*, 2016 WL 70583, at *2 (summarizing opinions of DEA pharmacologist – Dr. Jordan Trecki; Dr. Nicholas Cozzi – a pharmacologist and professor at Univ. of Wisconsin School of Medicine and Public Health; Dr. Greg Dudley – chemist and professor at Florida State university).

¹¹⁷ See *id.* at *8; *United States v. Malone*, 828 F.3d 331 (5th Cir. 2016) (affirming district court’s finding, based upon animal studies, that THC is the most closely related substance to AM-2201; Dr. Cozzi testified that marijuana was the most closely related substance).

¹¹⁸ USSG §2D1.1, comment. (n.6(C)). See *Hossain*, 2016 WL 70583, at *3–4; *Tebbetts*, No. 5:12-CV-567, at 15; *Ramos*, 814 F.3d at 919–20; *id.* at 921–22 (J. Bright, dissenting).

¹¹⁹ USSG §2D1.1, comment. (n.8(D)).

The table acknowledges that substances containing THC and plant material are less serious than a substance that contains THC, other chemicals, and plant material (hashish oil), or pure THC. Similarly, the guidelines should acknowledge that substances containing synthetic cannabinoids that also contain dried, shredded plant material or other liquids that are not controlled substances are less serious than substances that contain nothing but pure synthetic cannabinoids.

The fact that these drugs are described as “synthetic marijuana”¹²⁰ and that the Drug Enforcement Administration has acknowledged that these drugs are sold in bags of dried leaves, smoked, and have psychological effects similar to marijuana further supports using a 1:1 marijuana ratio than a 1:167 ratio.¹²¹ It would be anomalous to equate a substance used a substitute for marijuana as pure THC rather than as marijuana.

A blanket ratio of 1:167 for all synthetic cannabinoids also would result in treating dissimilarly situated defendants similarly. As one sample sentencing memorandum explains:

[C]onsider Defendant A—convicted of possessing with intent to distribute a kilogram of Mr. Happy . . .—and Defendant B—convicted of possessing with intent to distribute a kilogram of pure UR-144 or XLR-11, the active synthetic cannabinoids contained in Mr. Happy. Under the position of the Government, both would be equated to a 1:167 marijuana equivalency and sentenced based on 167 kilograms of marijuana (base offense level 26). However, Defendant B intended to spray the kilogram of pure UR-144 or XLR-11 he possessed onto a green leafy substance to create numerous kilograms of Mr. Happy for distribution. Defendant B just happened to be arrested before he could do so. If he had been arrested after he had done so, he would then be sentenced based on the 1:167 ratio applied to the many kilograms of Mr. Happy created.^{fn} The 1:167 ratio should be reserved for persons convicted of offenses involving the pure synthetic cannabinoid and the 1:1 ratio should be used for persons convicted with respect to the final product.

^{fn} How many kilograms of Mr. Happy could be created with a kilogram of UR-144 or XLR-11 cannot be determined without knowing the purity/concentration for Mr. Happy. However, based on the logic of the Guidelines, it could be assumed to be approximately 167 kilograms. Thus, Defendant B, if arrested after he creates the Mr. Happy, would have 167 kilograms of Mr. Happy, to which the 1:167 ratio would be applied under the Government’s theory, for a marijuana equivalency of 27,889 kilograms, or base offense level 36, an increase of 10 levels.

¹²⁰ *United States v. McKnight*, 662 F. App’x 479, 485 (8th Cir. 2016).

¹²¹ Drug Enforcement Administration, *Drug Fact Sheet: K2 or Spice*, https://www.dea.gov/druginfo/drug_data_sheets/K2_Spice.pdf

Troy Stabenow, *Sample Sentencing Memorandum for Downward Variance Based on 167:1 Synthetic THC Conversion*, 5B West's Fed. Forms, District Courts-Criminal §91:50.80, at n.2 (5th ed.) (May 2016).

In short, even if THC were the most closely related substance to the active ingredient in products containing synthetic cannabinoids, it does not mean it is the best substitute for all synthetic cannabinoids.¹²²

V. The Commission Should Revisit the Ratio for THC

The Commission should revisit the THC ratio because both defense and government experts agree that “there was no scientific basis for the 1:167 ratio used to convert THC into marijuana.”¹²³ Judge Middlebrooks recently explained the problem:

In considering the THC to marijuana ratio, I find it troubling that there does not seem to be any reason behind the 1:167 ratio. Although I asked each of the experts at the hearing, no one could provide me with a reason for this ratio, which has major implications in determining the base level offense. After my own research and a phone call to the Sentencing Commission, I still could find no basis for this ratio. It appears to have been included in the first set of Guidelines in 1987, with no published explanation. While a sentence must reflect the seriousness of the offense to provide just punishment, a sentence based on a range that seems to have no cognizable basis is not just.

At the hearing, I heard testimony from Dr. Cozzi regarding a more appropriate ratio for THC to marijuana:

“[S]aying that one gram of THC is equal to 167 grams of marijuana is like saying 167 grams of marijuana contains a gram of THC. That's what equivalence means. But if you calculate what percentage of THC that is on the weight, you take the one [and] divide it by 167, you get 0.6. So 0.6 percent of the total weight [of the marijuana] is THC. That's completely unrealistic in terms of psychoactive marijuana. We know from Government studies that the average THC content in marijuana today is over 14 percent. So the ratio should be one to seven, not one to 167.”

United States v. Hossain, 2016 WL 70583, at *5–6 (S.D. Fla. Jan. 5, 2016).

¹²² *Hossain*, 2016 WL 70583, at *10.

¹²³ *Malone*, 828 F.3d at 336 (noting that the government's expert, Dr. Jordan Trecki, and the defense expert, Dr. Nicholas Cozzi, agreed “there was no scientific basis for the 1:167 ratio used to convert THC into marijuana”).

Honorable William H. Pryor

March 10, 2017

Page 33

VI. Conclusion

As always, we appreciate the opportunity to submit comments on the Commission's work. We look forward to continuing to work with the Commission on matters related to federal sentencing policy and remain hopeful that the Commission will revisit the drug guidelines and focus on important factors like dosage and direct harms rather than using the weight of inactive ingredients to increase sentence length.

Very truly yours,

/s/ Marjorie Meyers

Marjorie Meyers

Federal Public Defender

Chair, Federal Defender Sentencing Guidelines Committee

cc: Rachel E. Barkow, Commissioner
Jonathan J. Wroblewski, Commissioner *Ex Officio*
J. Patricia Wilson Smoot, Commissioner *Ex Officio*
Kenneth Cohen, Staff Director
Kathleen Cooper Grilli, General Counsel

Appendix A - Transcript of Hearing, <i>United States v. McCarthy</i> , No. 1:13-cr-00570-JBW (E.D.N.Y. Dec. 6-7, 2010).....	1
Appendix B - Transcript of Telephonic Deposition of Dr. John Halpern, <i>United States v. Chin Chong</i> , No. 1:13-CR-00570-JBW (E.D.N.Y. Aug. 22, 2014).....	402
Appendix C - Declaration of Dr. Gregory Dudley, <i>Chin Chong</i> (July 24, 2014).....	495
Appendix D - Declaration of Dr. Charles Grob, <i>Chin Chong</i> (July 24, 2014).....	500
Appendix E - Declaration of Charles S. Grob, <i>United States v. Thannavongsa</i> , 2:13-CR-00255-JAD-GWF (D. Nev. July 16, 2014).....	510
Appendix F - Declaration of Dr. Gregory Dudley (Tallahassee, Florida, July 24, 2014).....	531
Appendix G - Declaration of Dr. Anthony Decaprio, <i>Chin Chong</i> (July 24, 2014).....	536

Appendix A

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1 UNITED STATES DISTRICT COURT
1 SOUTHERN DISTRICT OF NEW YORK
2 -----x

2
3 UNITED STATES OF AMERICA

4 v. 09CR1136(WHP)

4
5 SEAN McCARTHY,
5 LARRY WARREN HOUGH,
6 Defendants.

6
7 -----x

8 New York, NY
8 December 6, 2010
9 10:10 a.m.
9

10 Before:

11 HON. WILLIAM H. PAULEY III
11
12 District Judge

12
13 APPEARANCES

13
14 PREET BHARARA
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15 Southern District of New York
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1 (Case called)

2 THE COURT: Good morning, I note the presence of the
3 defendant Mr. McCarthy at counsel table and I note the presence
4 of Mr. Hough as well. This matter is on for a hearing. Are
5 the parties ready to proceed.

6 MR. CHUNG: The government is ready.

7 MR. RORTY: We are, your Honor. There are two
8 preliminary matters I would like to discuss.

9 THE COURT: Go ahead.

10 MR. RORTY: The government filed a letter with this
11 court Friday afternoon, that is December 3. I wanted to make
12 sure the court has received that letter.

13 THE COURT: I have.

14 MR. RORTY: On Mr. McCarthy's behalf, we filed a
15 pleading, a motion to exclude extrinsic evidence of the defense
16 expert's conduct yesterday afternoon, a motion electronically
17 filed with two affidavits, I wanted to make sure the court
18 received that document.

19 THE COURT: I have not seen that. So, if you would be
20 kind enough to hand a copy up, I would appreciate it.

21 (Pause)

22 THE COURT: I assume I can review this as we proceed
23 or during a recess, but we are not going to get to this matter
24 immediately.

25 MR. RORTY: I think that's probably appropriate given

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1 that the court has not had a chance to review it. We are
2 prepared to take up the issue at any time the court feels is
3 appropriate. Perhaps after the break or before Dr. Halpern's
4 testimony would be the best time after the court has had a
5 chance to review our document.

6 THE COURT: That's fine.

7 You said there was another matter.

8 MR. RORTY: Before we call our first witness, I would
9 like a few minutes to give the court a road map of what we
10 think will occur over the next couple of days, an introduction
11 to Mr. McCarthy's evidence in this matter.

12 THE COURT: That's fine.

13 MR. RORTY: At our previous hearing the government
14 argued that there was no need for this proceeding because in
15 2001, the United States Sentencing Commission heard testimony
16 and took substantial evidence regarding the harms of MDMA. The
17 government at that point argued that that settled the issue of
18 whether a post-Kimbro policy variance might apply in this case.
19 That argument can now be dismissed because we are having this
20 hearing. The fact that the commission held proceedings cannot
21 control the issue.

22 The question before this court is whether or not the
23 conclusions drawn by the commission in 2001 are still valid.
24 If they are, then the offense level controls and the guidelines
25 apply. If those conclusions have been undermined by the decade

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1 of science that has occurred since that hearing, we would
2 submit that a variance in this case is necessary and
3 appropriate.

4 As the court will recall in notes from the papers,
5 the commission based all of its findings resulting in the
6 offense level on a couple of key assumptions. First, that MDMA
7 is extremely neurotoxic, that it causes cell death. Second,
8 that MDMA is more harmful than cocaine in several respects.

9 If at the end of this hearing the court concludes that
10 the commission erred in those assumptions and reaching those
11 conclusions, then we would say that pursuant to Kimbro, a
12 variance is necessary and appropriate in this case. We would
13 be talking then not about whether the court should vary but how
14 far. If the commission got it wrong, if those assumptions are
15 false, then the offense level is not appropriate and the
16 sentence commensurate with that offense level should not be
17 imposed, there should be a variance.

18 We think based on Dr. Curran's, Dr. Halpern's, and
19 indeed on Dr. Parrott's and Dr. Hanson's, Mr. Hanson's
20 testimony, there will be some consensus that the commission got
21 it wrong and that the question is how far did they get it
22 wrong, how wrong were they, particularly about neurotoxicity
23 and cocaine. We will then at the end of the hearing be
24 discussing what is the harm of MDMA in relation to cocaine and
25 other drugs and how neurotoxic is it to the extent it is

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1 neurotoxic, that it causes cell death.

2 The court will hear some scientific disagreement with
3 respect to the extent and nature of neurotoxicity and the harm
4 relative to cocaine. But I suspect that discussion will be
5 predicated on an understanding that the commission got it
6 wrong, that the extraordinary neurotoxicity found by the
7 commission has been disproved, and that MDMA is not more
8 harmful than cocaine. At the end of the hearing we will be
9 asking the court to vary and arguing that the extent of the
10 variance should find that MDMA is approximately as harmful as
11 marijuana. But we expect that the scope of that argument at
12 the conclusion of the hearing will simply be about the extent
13 of the necessary variance called for in this case.

14 We are now prepared to call Dr. Valerie Curran.
15 Mr. Michelman will conduct that examination.

16 THE COURT: Very well.

17 HELEN VALERIE CURRAN,

18 called as a witness by the Defendants,

19 having been duly sworn, testified as follows:

20 DIRECT EXAMINATION

21 BY MR. MICHELMAN:

22 Q. Could you please tell the court your current title.

23 A. I am currently professor of psychopharmacology at
24 University College, London.

25 Q. Could you describe your main job responsibilities in that

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0C64MCC1 Curran - direct

1 role.

2 A. I am director of the clinical psychopharmacology unit. I
3 am an academic. I have students. I mainly do research. I
4 also am a clinical psychologist and a research lead at the
5 national health service, a series of clinics giving drug
6 treatment to addicts.

7 Q. Could you describe some of your professional associations
8 and activities?

9 A. Yes. I am a member of Council of British Association of
10 Psychopharmacology. I am a member of the U.K. Independent
11 Scientific Committee on Drugs. I am a member of several other
12 societies to do with addiction. I am also principal editor of
13 the major journal in the field, unfortunately also called
14 Psychopharmacology.

15 Q. Could you tell the court what degrees you hold.

16 A. I have a bachelor's and a master's degree from Cambridge
17 University and a PhD from London University and professional
18 qualifications from the British Psychological Society.

19 Q. Describe your area of research expertise.

20 A. My research concerns the cognitive and mood effects of
21 drugs acting on the brain.

22 Q. Tell us the sources of the funding for your research.

23 A. Yes. My current funding is mostly government, mainly the
24 Medical Research Council, also the Economic and Social Research
25 Council in the U.K. I also get money, small amounts of money

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1 from various charities, including the Beckley Foundation and
2 the Alcohol and Education Research Council.

3 Q. It sounds like the bulk of your funding is from the
4 government.

5 A. Yes, nearly all of it.

6 Q. Do you have any experience testifying in court?

7 A. I have only been in court twice, once with a mass
8 litigation for the crown against pharmaceutical companies
9 producing benzodiazepine, like Xanax and Valium, where a large
10 case was taken forward against companies that produced them,
11 and the second case was in the case of drug-assisted rape where
12 again I acted on behalf of prosecution. I have done a lot of
13 legal reports and I also sit on government committees such as
14 the Ministry of Defense Ethics Committee where my expertise on
15 drugs abuse is used.

16 Q. How long have you researched on MDMA?

17 A. MDMA, 14 years.

18 Q. How long have you researched on marijuana?

19 A. About 12 years.

20 Q. How long have you researched on ketamine?

21 A. On ketamine, 11 years.

22 Q. What types of work have you done on MDMA?

23 A. I have done studies looking at the variation in the effects
24 of MDMA from the night people take it across the following
25 days. I have done studies looking at the long-term effects of

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1 MDMA in users and especially started looking at what happens
2 when people stop taking the drug and following up for a period
3 of at least a year afterwards to see what happens to their
4 functioning when they have stopped, and those studies have
5 included brain imaging studies.

6 Q. Briefly describe your work on marijuana or the nature of
7 it.

8 A. Yes. My work on marijuana has been looking again at people
9 using it, but also laboratory studies where we administer the
10 active agreement in marijuana, THC. Our work is particularly
11 focused on how the different ingredients in marijuana affect a
12 person's likelihood for developing psychosis or addiction or
13 memory impairment. Again, we do brain imaging and other sorts
14 of studies.

15 Q. Describe the nature of your work on ketamine.

16 A. With ketamine we use ketamine as a model of psychosis
17 because it produces psychotic effects in healthy people like
18 you and me. So we do a lot of work in the hospital where we
19 administer it, but we also work with people who take the drug
20 recreationally, and in the U.K. certainly there is a subgroup
21 of addicts to ketamine nowadays. We work with them and try to
22 help them stop and look at the effects again on memory and
23 brain imaging and mood.

24 MR. MICHELMAN: Your Honor, the parties have agreed,
25 essentially stipulated that all the witnesses are expert. I

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1 will move into the substance of their conclusions, with the
2 court's permission.

3 THE COURT: That's fine, Mr. Michelman.

4 Q. Dr. Curran, I would like to start just in order to give a
5 road map of your testimony to summarize briefly the conclusions
6 you have come to, then we will talk about them in more detail.

7 We have asked you here to discuss the evolution of
8 research regarding MDMA and the harms of MDMA over the last 10
9 years. We have also asked you to form an opinion about the
10 validity of the science in the 2001 MDMA report to Congress by
11 the U.S. Sentencing Commission. And we have also asked you to
12 use your expertise across several drugs including marijuana and
13 ketamine to compare MDMA to those other drugs. I would like to
14 ask briefly about each of your conclusions in those areas.

15 Could you please give us your summary conclusions
16 about the evolution of the field of MDMA research in the past
17 decade.

18 A. Since 2001, the field has moved on quite a lot. In 2001,
19 there had been studies that were very influential in that
20 report where monkeys particularly had been given very, very
21 high doses of MDMA and the report was concerned about those as
22 we all were.

23 Since then there have been at least five different
24 kinds of advances. There have been new studies now where
25 people are followed from the time before they ever used MDMA

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1 and then reassessed after they used it. It's been much more
2 informative than a lot of previous studies and had a lot of
3 methodological confounds in part of the 2001 report. There
4 have been studies on recovery, what happens when people stop
5 using MDMA.

6 There have been a lot more animal studies. Before
7 2001 virtually all the studies injected toxic, enormous doses
8 of MDMA into the animals, which is not at all like how MDMA
9 users take the drug. Since 2001 there have been studies trying
10 to make more in animals what humans do, letting animals
11 self-administer MDMA. There have been two other developments.
12 There has been a whole range of acute studies where healthy
13 people in the labs are given doses of MDMA, often in comparison
14 with alcohol or with marijuana. So we can be really sure that
15 those are proper studies, placebo-controlled trials.

16 Finally, there's been some advancement as you would
17 expect in technology over the last decade where the imaging
18 tools that we have have got better, how we can see what happens
19 to serotonin in the brain, we have more options, and also the
20 use of technology like hair, for example. Your hair grows a
21 centimeter a month, and in your hair you can see what drugs you
22 have taken over those months. So instead of relying on people
23 saying, yes, I did Ecstasy the other night, it might not have
24 been, so you can actually see for sure what drugs that person
25 has taken.

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1 So I think all of those together and awareness of the
2 dosage issue unfortunately has changed science opinion since
3 2001.

4 Q. We will get into each of those concepts a little more
5 later. Give us your summary conclusion about the harmfulness
6 of MDMA to humans based on the current status of research.

7 A. On the basis of current state of research, MDMA is harmful,
8 it causes death in a very small number of people, and in the
9 U.K., for example, 10 people a year die from Ecstasy, 22 a year
10 die from cocaine, 187 a year die from heroin, and 150 die on a
11 year in bicycle accidents being run over. Death is one aspect;
12 it's rare.

13 I have also studies put together would show that in
14 people who are currently using MDMA, they show a small but
15 significant statistically impairment in their memory. When
16 they give up using, most studies show that impairment is no
17 longer there. Indeed, when they are currently using, it's so
18 tiny -- do you want me to go into this now.

19 Q. No.

20 A. And the brain imaging later.

21 Q. Do finish your thought.

22 A. The brain imaging studies have shown while people are
23 taking Ecstasy or MDMA, there is a reduction, a marker of a
24 brain chemical called serotonin which I hope I have time to
25 explain. Your brain is like an electrochemical soup where

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1 electrical signals are sent down from a nerve cell and to
2 communicate to the next nerve cell in the chain they have to
3 release a chemical. The chemical that is important with
4 Ecstasy is serotonin.

5 What normally happens is that the brain is a very
6 ecological system. That serotonin is then taken back into the
7 cell by something called a serotonin transporter. If you look
8 at the brain of humans who have used Ecstasy, you see a
9 reduction in the serotonin transporters while people are
10 currently using. Of all the studies that looked at people
11 after they have given up using this drug for a year, that's
12 normalized in 9 out of 10 of the studies. So we don't think it
13 has long-term effects on the human brain.

14 Q. Can you give us your summary conclusion about the validity
15 of the science behind the 2001 MDMA report to Congress by the
16 U.S. Sentencing Commission.

17 A. The validity of the science, a lot of it was based on
18 giving these doses, 5 milligrams per kilogram, to monkeys, also
19 similar doses in rats, twice a day for 4 days. So if you think
20 about what that means for a human, you are talking about 700
21 milligrams of Ecstasy on each of 4 days. Now, 95 percent of
22 Ecstasy users take the drug. They take 100 milligrams,
23 sometimes a bit more, sometimes a bit less, but they take it
24 once or twice a month.

25 So, scientists reflecting back to 2001, will say those

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1 studies were not applicable, it was not valid to generalize
2 from those incredibly toxic doses in animals to humans who use
3 100 milligrams once or twice a month. It's like trying to
4 extrapolate from giving a young person, making them drink a
5 bottle of whiskey or bourbon a day for 4 days meant something
6 to college students having a few drinks. It's out of
7 proportion; it became exaggerated.

8 Q. What is your summary conclusion about the harmfulness of
9 MDMA relative to ketamine and marijuana respectively?

10 A. I think for various reasons, which hopefully we will go
11 into, the evidence very much says that Ecstasy, MDMA, is less
12 harmful than either ketamine or marijuana.

13 Q. So let's delve into each of these areas a in a little more
14 detail. First could you just tell the court generally what is
15 MDMA?

16 A. MDMA is a stimulant drug which in users the effects are
17 described as what we call the three Es; euphoria, energy, and
18 empathy. The major pharmacological effects of MDMA is to
19 release serotonin that's stored in the braincells, block its
20 reuptake and also reduce the enzyme, the activity of the enzyme
21 the brain needs to create more serotonin from our diet, so that
22 the massive release on the night someone takes Ecstasy is then
23 followed by a period of a few days where the brain then
24 recreates the same levels.

25 Q. If I could try help put that in layman's terms, what I hear

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1 you saying, correct me if I am misunderstanding, is that MDMA
2 causes the brain to release a great deal of serotonin which
3 makes people happy and levels are depleted for a couple of
4 days, and then they return to normal?

5 A. Absolutely, yes.

6 Q. Can you describe some of the challenges of studying MDMA?

7 A. Sure. If you are studying any medicine particularly, I
8 also work on medicines prescribed in psychiatry, the normal
9 approach, what we call the gold standard, is you do a
10 randomized control trial. You split say the courtroom in half
11 and give people on the left MDMA every Saturday night for a
12 year, and the people on the right, you give them a placebo, a
13 dummy pill every day for a year.

14 Because it was randomized, I said left and right, I
15 shouldn't have, it was a randomized treatment, then you can
16 presume that everyone was fairly similar to begin with and what
17 effects you observe a year later are actually caused by the
18 drug. If the drug is illegal, you can't do that, so you have
19 to think of other ways of comparing groups of people who use
20 and don't use to try to understand what the effects of this
21 drug are.

22 That creates a lot of problems because, as you can
23 image, the people who use Ecstasy, I am thinking of all the
24 16-year-olds you know, some of them might be more
25 sensation-seeking, party-going, whatever, and more likely to

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1 use the drug where others might be much more into baseball or
2 schoolwork and less likely to use the drug. So when you
3 compare them, the people who are using Ecstasy to the people
4 who are not, you are not comparing like to like because they
5 were different to begin with.

6 There are also problems to doing this because you
7 don't know because if they bought a pill from a dealer and they
8 don't know how much Ecstasy is in it or if it is actually
9 Ecstasy. The big problem is that 99.9 percent of Ecstasy users
10 also use a wide range of other drugs. All of them use
11 cannabis, marijuana, sorry, and there is variety of other
12 compounds like cannabis and 95 percent would be using alcohol
13 as well.

14 So when you are comparing the group who used Ecstasy
15 with the group who didn't, you also have to make sure that you
16 are covering those other drugs. We know that marijuana can
17 cause memory impairment as well. We know that alcohol has a
18 memory-impairing effect.

19 Q. I have the heard term confounds used in connection with
20 scientific studies. Are the types of issues you are describing
21 with the use of other drugs and the preexisting dispositions of
22 the subjects, those would be referred to as confounds?

23 A. Yes.

24 Q. You mentioned that in 2001, there were a lot of studies of
25 MDMA done on animals. Could you tell us what if any drawbacks

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1 there might be to generalizing from the animal studies to the
2 human studies, to harm to human beings?

3 A. With the animal studies you can be sure about causation
4 because you are actually giving them the drug and you give them
5 a placebo. The drawback is, as I was saying, the animal
6 studies before 2001 were all giving these incredibly high toxic
7 doses to animals twice a day for 4 days and injected, which you
8 can't then generalize to a human who uses a pill once or twice
9 a month. It's a completely different thing.

10 Injecting a drug has different effects from taking it
11 if through the mouth and metabolizing it and absorbing it
12 through the gut and into the brain. There is also the issue of
13 metabolism. How humans metabolize MDMA is very different from
14 how rats and monkeys metabolize it which makes generalization
15 not possible directly from one to the other.

16 Some people have argued you can do a thing called
17 interspecies scaling, which is simply an adjustment for weight
18 and it means nothing. You can't do that. You have to equate
19 patterns of consumption. You have to equate how that drug is
20 metabolized. The metabolites differ across different species.
21 I think the 2001 report took that argument which has since been
22 very, very much criticized and no longer holds.

23 Q. Can you describe the difference between impairment and
24 brain damage.

25 A. Impairment usually refers to a functional impairment. It's

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1 an important issue with MDMA because even if you look at the
2 animals studies with rats or with monkeys where they achieved
3 massive depletion of serotonin, like 70 to 90 percent, huge,
4 something you would never see in a human, the rats and monkeys
5 behaved normally. It didn't have any effect on them.

6 Even if they showed brain damage of the sort that was
7 argued in the monkey studies, there was no impact of that on
8 the monkey or the rat's behavior. It didn't make them forget.
9 It didn't do anything at all. They carried on as normal. So,
10 the brain damage if you like had no functional consequences.

11 Q. It sounds like there has been a great deal of work in the
12 field in the past ten years and you have described some of the
13 ways in which the field has advanced. In attempting to get our
14 hands around the body of work that has occurred, what types of
15 reviews of the literature might a scientist look to assess the
16 state of the field as a whole?

17 A. There is a gold standard which is called a systematic
18 review. It's the basis in the U.K., probably here too, of all
19 kinds of treatment guidelines for medicine throughout the
20 country. So there are two systems, the Cochrane reviews and
21 the National Institute for Clinical Excellence, where all
22 guidelines by all doctors in the U.K. have to follow these.
23 These are all based on systematic reviews, whatever the
24 illness, whatever the condition. That's a gold standard of
25 medicine as well. It's a way of summarizing the vast body of

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1 literature and working out what key elements are in the
2 efficacy of different treatments.

3 Q. Could you explain whether some systematic reviews are
4 better than others?

5 A. Some systematic reviews are better than others. It depends
6 on how well they followed the guidelines and how absolutely
7 clear they are about the criteria for selecting which studies
8 to review, analyzing the quality or the stages that you need to
9 integrate in an unbiased way a set of literature.

10 Q. What is a meta-analysis?

11 A. Within a systematic review, it could be that many, many
12 different studies have looked for the same outcome. So often
13 in medicine it's the years you live after being diagnosed with
14 cancer or something. You can do similar things, say, with the
15 MDMA literature if you take a measure that has been used many,
16 many times by many, many studies. So for example, how well you
17 remember a list of words, there have been dozens and dozens of
18 studies. So a meta-analysis allows you to put together all the
19 information you have. It gives you a lot stronger basis for
20 saying whether there is an effect of the drug or there is not.

21 Not only that, well, it gives you an estimate of how
22 big that difference is. So if your Ecstasy user is over here
23 and your nonusers are here, is the difference between them this
24 much, this much, you can map it out. You can also look at all
25 the confounds that would affect those results.

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1 Q. Are there any particularly good systematic reviews and
2 meta-analyses in the field of the MDMA literature?

3 A. There is one, the Rogers review which looked at the harms
4 of Ecstasy; basically he asked one question, what are the harms
5 of MDMA.

6 Q. That was one of the papers that you identified and we
7 submitted to the court?

8 A. Yes.

9 Q. That was the giant 300-page one?

10 A. Yes.

11 Q. Why was that review in particular good?

12 A. Because it followed the absolute gold standard guidelines
13 for doing a systematic review so, all the criteria for
14 including one study or not including another are clearly laid
15 out and the whole idea is that these reviews are valid, because
16 someone completely indifferent can come along and based on the
17 same information, select the same studies and reach the same
18 conclusions.

19 Q. Even though it's not a clinical study, its results can be
20 replicated?

21 A. Absolutely, yes. Its strength is that it takes into
22 account all the studies that have been done wherever in the
23 world and brings them all together and gives a much more
24 powerful way of looking at possible confounds and helping us
25 understand why perhaps marijuana might interact with Ecstasy in

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1 some studies and not others.

2 Q. In what other ways might the literature be reviewed?

3 A. The traditional old-fashioned way of doing it was to do
4 what's called a narrative review whereby a person brings
5 together, or several people bring together, things they are
6 thinking about, select studies to include in the review, but
7 don't put down criteria for including them or excluding them.
8 It's more like they include which studies they want and there
9 is no systematic way of reaching conclusions from that because
10 there is nothing laid down in advance. So they are very
11 whimsical and can be rather biased.

12 Q. Can you give us an example among the studies that have been
13 submitted to the court of a narrative review of the type you
14 describe?

15 A. Well, Dr. Parrott submitted a review published in 2001
16 which reviewed 15 years of MDMA research. That's a narrative
17 review. He chose the studies that he wished to include. In
18 fact, there were over 20 of his own studies in there. That's
19 normal; people are a bit biased toward their own work. He also
20 included discussion of papers that were not published, of
21 conference abstracts, all things that would never have been
22 allowed into a meta-analysis.

23 For example, in that review, Dr. Parrott very nicely
24 lays out a table of all the studies that have shown a memory
25 deficit in Ecstasy users but he didn't also lay out all the

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1 studies that have not shown a memory deficit. So a narrative
2 review is much more biased; it's not a systematic evaluation of
3 the evidence.

4 Q. It sounds like it's important to have criteria to decide
5 which studies to include in a review and how heavily to weight
6 them. What would you describe as some of the hallmarks of some
7 of the best studies in the MDMA field?

8 A. The hallmarks, and they are exactly very clinistic in the
9 criteria for a systematic review, which are, you very carefully
10 match your groups of Ecstasy users for every other drug that
11 they could have taken and the amounts of Ecstasy used, the age
12 they started using Ecstasy, their educational level, their
13 intelligence, gender, lots and lots of different factors. I am
14 talking about studies comparing groups. There are much better
15 designs that can be used. Do you want me to talk about those?

16 Q. Sure.

17 A. Most studies compared one group of Ecstasy users with one
18 group of people who use other drugs but not Ecstasy and then
19 people who use legal drugs. And there are lots and lost of
20 confounds when comparing those groups. Other studies that have
21 been done since 2001 have taken a whole group of young people
22 who are not currently using Ecstasy, say when they are 16, 17,
23 and then they follow those same individuals through, and some
24 of them will inevitably start using Ecstasy in that period.

25 That's a very good way of controlling for confounds,

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1 because you have information on all those individuals before
2 they ever used the drug. So you can check they are the same
3 kind of people with a similar intelligence, simple educational
4 background, similar kind of secure family, similar schools. If
5 half of them then use Ecstasy, you can compare one/half with
6 the other later on.

7 Q. That type of study you just described of following a group
8 of people, the same group of people over a period of time, I
9 understand that is called a perspective study?

10 A. Yes.

11 Q. So you mentioned the hallmarks of the best studies being
12 the controlling for key variables and the perspective study?

13 A. Yes.

14 Q. Any others?

15 A. Yes. There have been some very nice studies since 2001.
16 For example, there is one in Holland where they started
17 assessing children in 1983 before Ecstasy was ever, before MDMA
18 was ever in use in Holland. That information on children from
19 age 2, 3, 4, they followed them through for, it was probably
20 age 6 to 9, they followed them through for a period of 16
21 years.

22 What they found was that some of those children, a
23 small percentage, around 9 percent, did actually start using
24 MDMA when they were teenagers. So they could compare them then
25 with people in the same cohort, and these are big numbers, like

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1 nearly 2,000 children, who have not used MDMA. When you do
2 that, what you find is that any sort of problems to do with
3 anxiety or depression, they were actually there in the majority
4 of children before they ever used Ecstasy. In fact, if you
5 were in a clinical group when you were a child having any
6 anxiety or depression problems, you were 2.2 times as likely to
7 then go on and use Ecstasy.

8 Q. I infer from what you said earlier about the doses that
9 used to be given to animals, that a good study would also use
10 an appropriate dose of MDMA?

11 A. Yes.

12 Q. As of 2001, how many studies are you aware of that met the
13 criteria you have just described, that is, human studies,
14 looking prospectively, controlling for the important variables,
15 and with a dose comparable to what a human would take?

16 A. There were no human studies like that in 2001.

17 Q. But today there have been?

18 A. Today, yes, in Holland again, the large multimillion dollar
19 study called the NextC study that followed people through.

20 Q. Just for the court's benefit could you identify or spell
21 that out, the NextC study.

22 A. N-E-X-T-C.

23 Q. Was that study the source of any of the papers that you
24 submitted to the court?

25 A. It was; it was the source of the Schilt, et al., paper.

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0C6UMCC2 Curran - direct

1 Q. So now that we have talked about some of the methodological
2 advances and some of the recent studies, let's talk about what
3 they have actually shown us. Do the best studies like the
4 NextC study and the Rogers meta-analysis yield similar
5 findings?

6 A. I think that is what is interesting, given the field and
7 the methodological problem, I think, as scientists, you want to
8 see things coming together and saying the same thing. And what
9 the meta-analysis says is that there is a small but significant
10 memory deficit in current users. The Schilt perspective also
11 shows that. So that kind of increases our confidence that
12 there is something there. But if you look at both of them,
13 just because it is statistically significant doesn't mean that
14 it has any impacts in the real world.

15 Should I try to explain what statistical significance
16 means?

17 MR. MICHAELMAN: I will actually ask the Court. Would
18 that be helpful or does the distinction between statistical
19 significance and size or scope, does that become clear from the
20 witness's testimony?

21 THE COURT: I think that I have a general sense of
22 statistical significance, but the question here is what is the
23 power of it. And I think it would be perfectly fine to make
24 further inquiry of the witness and make the record here.

25 MR. MICHAELMAN: Thank you, your Honor.

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0C6UMCC2 Curran - direct

1 BY MR. MICHAELMAN:

2 Q. So, Dr. Curran, could you describe when you talk about a
3 finding of memory impairment as being statistically significant
4 yet also small at the same time? Could you describe what those
5 two things mean and how they can be true at the same time?
6 A. Shall I do it in terms of -- if we look at the actual
7 research that we have been discussing, the meta-analysis by
8 Rogers and the NextC study, they both concur in showing that
9 the size of the memory effect is roughly -- well, in English,
10 if you were given 30 items to get from a store, so you are
11 going shopping, if you used Ecstasy then you would probably
12 forget one of those items. You would remember 29 out of 30,
13 whereas if you had not used Ecstasy, it is more like 30 out of
14 30. Those are the effect sizes we are talking about. We are
15 much more used to talking about memory, talking about growth
16 memory with Alzheimer's and things like this. But the Ecstasy
17 users in the Dutch studies were showing such a small effect
18 size, this sort of one word out of 30, that people generally
19 feel that it is not going to impact on day-to-day life.

20 You could have like, for example, the Toronto Blue
21 Jays being a certain height and the Yankees being a certain
22 height. And it could be that just by chance, you look at the
23 difference between the heights in the two teams, and the
24 Toronto Blue Jays are a quarter of an inch smaller, so that
25 would be significant as long as they were more roughly

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1 distributed the same. So it would be specifically important,
2 not significant. But I am not very good on baseball, but would
3 that mean anything about how they might do in a tournament? It
4 is a difference between a statistical significance and
5 something actually being meaningful in real life.

6 Q. Thank you.

7 What do the NextC and Rogers studies tell us about the
8 long-term effects of MDMA on humans?

9 A. The Rogers meta-analysis simply says that there is a very,
10 very small effect size in memory long-term, meanwhile people
11 are still taking it.

12 Q. No, I mean, are there any other long-term effects that have
13 been shown by those studies that you have referred to?

14 A. Yes. The meta-analysis did show a very, very small effect
15 on symptom checklist.

16 Q. Could you explain what you mean by that?

17 A. Questionnaires of people on how anxious or depressed they
18 felt. It was an even smaller effect there than memory.

19 Q. Any other long-term effects that were found?

20 A. No. It was mostly different kinds of memory they were
21 talking about and then questionnaire measures of mood.

22 THE COURT: When we speak of long-term effects, Dr.
23 Curran, can you explain what connotes a long-term effect?

24 THE WITNESS: I think that we can divide it up into
25 the studies that were given the single dose of MDMA in the lab,

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1 so that is quite an acute effect. And then you have just after
2 someone has taken Ecstasy, you get a little dip in mood so that
3 is another little bit of time. And if someone has taken
4 Ecstasy for several occasions, then we talk about long-term
5 effects. Then after that, if that person then stops using the
6 drug, then we talk about recovery or abstinence effect. So it
7 is a timeline.

8 THE COURT: Thank you.

9 BY MR. MICHAELMAN:

10 Q. Actually, that is very helpful, and I would like to follow
11 up.

12 What have the studies you have mentioned, the NextC
13 study and the Rogers meta-analysis told us about the recovery
14 or the persistence of the effects after one stops taking MDMA?

15 A. Well, the NextC study doesn't really talk to that yet
16 because it is still quite new and it not published and hasn't
17 followed those people through to stopping, so we don't know.
18 The Rogers review done in 2006 had an odd -- what they thought
19 was an odd effect, whereby some studies had shown more of an
20 impairment in ex-users.

21 Q. I'm sorry. I may be confused about the date of the Rogers
22 study. I just want to make sure we are talking about the same
23 one. The one that I have in my binder is 2009. I think that's
24 the one that we submitted. Were there two?

25 A. I thought it was before that. The meta-analysis was

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1 certainly done.

2 Q. This is "The Harmful Health Effects of Recreational
3 Ecstasy: A Systematic Review"?

4 A. Yes.

5 Q. The copy I have says 2009.

6 A. Yes. It might well be, but the studies included in it only
7 go up to 2006 or 7 because you have to take a cut-off before --
8 it is a massive amount of work to do a systematic review, and
9 you have a cut-off date, and you will find it is 2006.

10 Q. That makes sense.

11 Let's look for specific outcome. Does any study show
12 a persistent damage over time after a user abstains from
13 Ecstasy?

14 A. Well, in terms of the neuroimaging studies, Reneman, who is
15 a top brain researcher in Amsterdam, did a review in 2006 and
16 four out of five studies at that point showed recovery in terms
17 of serotonin in the brain. And since then, there have been
18 another five studies, all showing recovery either with stopping
19 or recovery less steep as people have reduced their dose. I
20 cannot remember the one study in the Reneman review that hadn't
21 shown it. I think it is nine out of ten have.

22 Q. So, in general, somebody could use Ecstasy for a period of
23 time, stop use and their brain would, more or less, return to
24 normal?

25 A. I don't think their brain was abnormal to begin with, it

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1 was just this marker of serotonin transporters that returned to
2 normal. We don't know if that toxicity -- you don't get the
3 cell death with MDMA.

4 Q. So in fact they have taken MDMA and they may not have had
5 much of a brain effect to begin with or a brain change whose
6 implications are unclear, and then their brain returns to
7 normal?

8 A. Yes. It could have just been, rather than the toxic
9 effect, the brain kind of looks after itself. It tries to keep
10 homeostasis. It tries to keep its functions working. So with
11 any drug, the brain will adapt and down regulate parts of
12 receptors and important aspects of neurons. And then when you
13 take that drug away, the brain readapts. So a lot of people
14 would say there's no evidence in humans of toxicity at all
15 because it just looks like a normal response to the brain.

16 If you are in pain, had a major operation and your
17 doctor gives you morphine to help, then your brain is going to
18 adapt its opioid system in terms of receptors in response to
19 that. And when you come out of hospital and they take you off
20 your painkillers, you are going to have a slight withdrawal
21 problem because your brain is readapting again to the absence
22 of the drug. So this is a key thing that a lot of the human
23 researchers feel that there is never a toxicity shown, it could
24 simply be neuroadaptation.

25 Q. Can you compare MDMA to other drugs in terms of

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1 neuroadaptations, that is, do humans successfully adapt and
2 return to normal after all drugs or are some -- do some create
3 permanent changes or damage?

4 A. I think it depends hugely on the drug, hugely on the dose,
5 hugely on how often you take it and probably other factors
6 too -- how vulnerable you are. We all differ genetically. We
7 differ in lots of other ways. So that if you are taking heroin
8 or crack cocaine every day for years and years of your life,
9 you probably get to a point -- we know you get to the point
10 where there is quite severe damage that may never recover.

11 Q. So MDMA wouldn't be in the same category as drugs from
12 which one can take to the point one doesn't recover?

13 A. I mean, it is incredibly rare that anyone would use a drug
14 like this every day or heavily. It is just not the normal
15 pattern. So you wouldn't get that same damage. Something like
16 methamphetamine can have clearly toxic effects on the brain
17 that are long-lasting.

18 Q. Let's talk about another effect sometimes claimed for MDMA.
19 Is MDMA addictive?

20 A. No. Categorically. In virtually all of the sort of papers
21 that have mentioned addiction and there have been several
22 recent ones by Linda Cotler. The pattern of use of Ecstasy by
23 virtually everyone, 98 percent, is once or twice a month.

24 Last week I was at this drug clinic that I do the
25 research at where we have 1400 people in treatment. And I said

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1 to them, this thing has come up for a court case next week.
2 Can you just tell me who in treatment at the moment has a
3 primary Ecstasy problem? And they just laughed, you know.

4 Even the national treatment figure is less than 1
5 percent ever going with Ecstasy as a primary concern compared
6 to 8 percent with ordinary cocaine, not crack cocaine, and 14
7 percent with cannabis in drug treatment services in the U.K.

8 I mean, I can't imagine someone being addicted, I
9 mean, having treated addicts myself, you take a drug just once
10 or twice a month -- it is like saying if you went out for
11 dinner and had a few too many glasses of wine twice a month
12 with your friends, you are running a risk of addiction. It is
13 nonsense.

14 The reason this has come up is people have given like
15 questionnaire measures based on what the gold standard is in
16 psychiatry which is called the DSM. It is the statistical
17 manual for diagnosing anything from depression, schizophrenia,
18 substance abuse. Now, this doesn't have a category of Ecstasy
19 abuse, quite sensibly because none of us believe it, none of us
20 believe it could be dependent.

21 And even the new version of it that is coming out in
22 2012 won't have a special category of Ecstasy dependence. But
23 the way you diagnose dependence on other drugs in the DSM is
24 simply to say, is there evidence of tolerance, withdrawal,
25 using more and more often than you wanted to, getting in

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1 trouble with law -- those kinds of things.

2 For abuse, you only need to tick one of those and for
3 dependence you need to tick three. And we know that with
4 Ecstasy that people increase the dose they take over time so
5 that if they started off taking 75 milligrams, a year later
6 they might be taking 100. So that is seen as evidence of
7 tolerance. The other way tolerance is seen is you keep taking
8 the same dose but the effect reduces. So you would tick off
9 boxes for Ecstasy. We know the same thing happens with
10 alcohol. If you take the first time you had a beer, it was
11 probably when you were -- you got to be 21 here -- most people
12 would have a beer at 16. A small amount of beer then would
13 have had quite a big effect, and a couple of years later, you
14 probably take twice the amount. So tolerance is something that
15 happens with all drugs and the new DSM V will remove that as
16 being such a major criterion.

17 Q. You have suggested today overall in your testimony that the
18 harms of MDMA are, though statistically significant, fairly
19 minor. Are you aware of studies since 2001 that disagree with
20 you, that find greater harms than you have attributed to MDMA
21 today?

22 A. Yes. It would absolutely be the odd study here and there.
23 There is some strange study in Hong Kong where they showed big
24 differences, but I think that was an outlier.

25 So you are asking me, are there studies that disagree

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1 that the effects are small?

2 Q. Right.

3 A. You have to understand that in this field there is a huge
4 variation in the quality of studies. Some studies are
5 published in journals that are not very high-ranking and those
6 studies are often most confounded. But if you concentrate on
7 the quality publications, the quality studies, then I think you
8 never say scientists will agree, but I think that there is a
9 consensus, certainly, that we don't now see MDMA being as
10 impairing -- as we all worried about actually in 2001, and we
11 did worry about the studies that were available at that time,
12 but now we can look back with a much more informed view.

13 Q. And just to re-emphasize, when you say that some of the
14 studies showing harm would be confounded, you mean not
15 controlling for key variables?

16 A. For all the important variables.

17 Q. You spoke about your own view. It sounds like your own
18 view has evolved since 2001?

19 A. Yes, because part of the reason that my own work went into
20 the direction of looking at what happens to people when they
21 stop using the drugs was based on the same squirrel monkey
22 study by Ricaurte in 1999, which is a real concern for that
23 review where they have given squirrel monkeys huge doses of
24 MDMA in the way I said before, so twice a day for four days,
25 injected into the monkeys. And what they have done is they

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1 killed off those monkeys two weeks later and found there was a
2 loss of serotonin in the brain. And then they left the other
3 half live for seven years later and they found a lot of
4 recovery, but there was still evidence of less serotonin in
5 their brains.

6 So given that millions of people in the U.K., the
7 U.S., throughout Europe and other parts of the world were
8 taking this drug, there was a natural concern that there was
9 something very dangerous here. But now with all of the work
10 that has gone on in the last decade, we know that that was
11 unfounded, but it was still important to do the work to show
12 that it was wrong.

13 Q. Right. Let's move on to the 2001 report to Congress by the
14 United States sentencing commission. Are you familiar with
15 this report?

16 A. Yes, I have read it.

17 Q. And how did you become familiar with it?

18 A. Because you sent it to me.

19 Q. I would like to take you through some of the report's
20 claims and see if they still hold up today in light of the
21 current science.

22 The report says that MDMA is "neurotoxic." How does
23 the report seem to be using that word?

24 A. I think it is seeming to use the word based exactly on
25 these monkey studies I was just talking about in terms of loss

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1 of axons. They are not talking about death of brain cells
2 which is classic neurotoxicity. It is another kind.

3 What happens, this is a nerve cell. You get the long
4 slender fiber that comes out of it -- it is called the axon --
5 down which the electric current flows so that the chemical can
6 be transmitted to the next brain cell.

7 What that study in 2001 was showing, it had been kind
8 of clipped, shortened so that they call that axon loss. And
9 that was their index for neurotoxicity. We know that even with
10 the same study, that it grows back but sometimes in different
11 tree type patterns rather than in the longer slender pattern.

12 Q. If I am understanding you correctly, the report referred to
13 the loss of axons --

14 A. Yes.

15 Q. -- as its evidence of neurotoxicity but we know today that
16 the axons actually grow back?

17 A. They grow back but not in the same way, yes, in animals and
18 that is only following neurotoxic dosages. The 2001 report
19 also had a human study from the wife of the man who did the
20 monkey study showing that in a few Ecstasy users there was a
21 decreased level of these serotonin transporters in the human
22 brain. That study has been very much criticized since -- I
23 think it was at the time of the review as well. That study
24 then claimed that there was global loss of serotonin
25 transporters throughout the human brain.

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1 Now, if you look at studies done more recently, for
2 example, a study by Kish which was published in Brain recently,
3 and he controlled a lot of confounds that that original study
4 had never controlled for. He made sure it was real Ecstasy in
5 the hair. He made sure that they weren't under the influence
6 of any other drug. He matched everyone for intelligence and
7 addressed most of the confounds that we have discussed already.

8 And when he did the brain scan of the Ecstasy users
9 versus the others, he did actually find in current users that
10 in two areas of the brain there was a depletion of this
11 serotonin transporter, completely different from what the
12 original study had shown a global across the whole brain.

13 Here we are just talking about two very small effects,
14 the effect on the hippocampus which is what is really important
15 for human memory. It makes sense in terms of small effect
16 sizes for actual memory performance. But on studies showing,
17 which Kish refers to, that if you then take people and test
18 them again in the scanner over a year after they have stopped
19 using the drug, there is no difference.

20 So it seems to be now, the evidence as a whole is
21 showing very specific depletion of serotonin transporters in
22 human brains of people currently using, but much, much tinier
23 than was imagined in 2001. But if you test those same people
24 again after they have given up, there is no difference; you can
25 not tell the difference between them and people who have never

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1 used MDMA.

2 Q. For the record, the Kish study to which you refer is the
3 study in Brain in 2010?

4 A. Yes.

5 MR. MICHAELMAN: I will just point out for the Court's
6 benefit that that is one of the studies that the government
7 submitted to the Court in advance of this hearing.

8 Q. Getting back to the 2001 report, it mentions fatalities,
9 and you said that MDMA does cause deaths?

10 A. Yes.

11 Q. Can you remind us how often it does that?

12 A. Well, I have the U.K. figures, because the U.K. and U.S.A.
13 figures don't compare because we have different coroner
14 procedures.

15 In the U.K. there are 10 deaths a year that are known
16 to be due to Ecstasy, compared with 22 a year to cocaine and
17 187 a year to heroin and 150 to cycline. So, yes, it does
18 cause death, but it is relatively rare. And we know what the
19 problem is. When it does result in death, it is generally due
20 to hyperthermia or overheating and heat stroke. And there is
21 one other cause is hyponatremia where sodium levels drop in the
22 blood and that is largely because people have got very hot and
23 drunk too much water and they have swelling in the brain.

24 Q. The report claims a damage to working memory. Has that
25 been borne out by the subsequent science?

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1 A. I think working memory and episodic memory have been the
2 focus, so yes, there is a small effect. It is not as big.
3 Working memory is keeping information in your head while you
4 are manipulating it. And, again, there is a very small effect
5 size showing a difference. And, again, it has not been shown
6 in the more recent studies that have been more better
7 controlled.

8 Q. What about the term "suicide Tuesday" that the report
9 cites, seemly to indicate that users might be at risk of
10 suicide after they use?

11 A. It is hilarious. It was based on my work -- I have never
12 used that term and when I traced it back from the reporter,
13 they said it was the New Yorker magazine. So it was not a
14 scientific reference.

15 I know that the New Yorker magazine had translated
16 what I was talking about before, but after you take Ecstasy on
17 the night, you get a dip in mood a few days later which I
18 called the mid week glow, and lots of Ecstasy users call moody
19 Tuesday and suddenly the New Yorker was calling it suicide
20 Tuesday -- is all.

21 Q. But you are not aware then of any studies showing that MDMA
22 users tend to commit suicide several days after use?

23 A. There is something in the paper that has information about
24 that. Over the past 11 years there have been six suicides
25 associated with MDMA in the U.K., but that is over 11 years.

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1 Q. On page 18 of the report it says that MDMA may produce a
2 dysphoria which I take to be a depression, again citing the
3 work of Carl Jansen. Is that claim well founded?

4 A. I think at that point in the report it was saying that MDMA
5 can be addictive and produce dysphoria. And it cites this
6 paper by Jansen which I am sure they have not read because it
7 is a terrible paper. It has three cases of people they claim
8 to be addicted to Ecstasy.

9 One was an electrician, age 25 who was suffering from
10 posttraumatic stress disorder who used Ecstasy on the weekends
11 and used a bottle of Jack Daniels every day and claimed that
12 the Ecstasy stopped him from getting too drunk on the weekend
13 and counteracted the Jack Daniels.

14 Another one was a son of an alcoholic who was
15 dependent and was being treated for addiction to heroin and to
16 benzodiazapines and had been treated for the past three years
17 and then started injecting MDMA.

18 And the other one was a son of schizophrenic who
19 killed himself when he was 12, and the child was a daily
20 cannabis user who suffered a seizure when he took an enormous
21 amount of pills of Ecstasy in combination with amphetamine.

22 So to me, none of those speak to -- those are
23 problematic people, individuals who need help. Ecstasy is just
24 one of the issues. They all have horrendous problems.

25 Q. So I take it then from what you said, what you told us

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1 already today that would not be considered a well controlled
2 study?

3 A. That would not be considered a study. It wouldn't get into
4 the tabloids.

5 MR. MICHAELMAN: Just for the record, this is the
6 paper "Ecstasy (MDMA) Dependence" by Carl Jansen, 1999.

7 And for the record, I point out to the Court that that
8 was one of the studies submitted to the Court by the
9 government.

10 BY MR. MICHAELMAN:

11 Q. So speaking generally now, in hindsight, how would you
12 characterize the conclusions in the MDMA report by the
13 sentencing commission in 2001?

14 A. The conclusions they made?

15 Q. Yes.

16 A. They concluded that MDMA was worse than cocaine because it
17 was neurotoxic, and I think now we can reconsider that and,
18 also, we know that cocaine can be addictive where MDMA, I have
19 never seen any addict so I don't think it is possible, but
20 there will be always be some crazy drug users who uses all
21 sorts of drugs, but I don't think that MDMA is addictive.

22 The other conclusion they were saying was because it
23 was marketed to young school children. I think the problems --
24 certainly in the U.K. use of Ecstasy has gone out, as in Europe.
25 I think it has gone down a bit in the U.S. I haven't checked

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1 the epidemiology, but I know in the U.S., the biggest problem
2 emerging among eighth and tenth grade children is much more to
3 do with prescription pills than it had to do with Ecstasy
4 nowadays.

5 Q. In conclusion, could a reasonable factfinder, familiar with
6 the studies today reach the same conclusion as the 2001 report
7 reached about the harms of Ecstasy?

8 MR. CHUNG: Your Honor, I object. The use of the
9 words "reasonable factfinder," vague, legal conclusion.

10 MR. MICHAELMAN: I will rephrase.

11 THE COURT: Very well.

12 Q. Would any reasonable scientist familiar with the studies
13 reach the same conclusion today as in 2001 about the harms of
14 MDMA?

15 A. I think a well balanced scientist could not reach the same
16 conclusions.

17 Q. Thank you.

18 I would like to move on to one final topic for which
19 we have asked you here today, the comparison of MDMA to a
20 couple of other drugs you have worked with, marijuana and
21 ketamine.

22 Could you briefly introduce the Court to what is
23 ketamine and what are its principal effects?

24 A. Ketamine is used medically as an anesthetic but in animals
25 and children. It produces very profound impairments of memory.

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1 It can induce narcotic-like experiences where it has been
2 taken. And it can produce dependencies in some users. Some
3 use recreationally. Some go on to become dependent on
4 ketamine.

5 Q. What types of problems are associated with recreational
6 ketamine use?

7 A. The problems of recreational ketamine use are fairly minor
8 compared to what happens -- it all depends on the dosage and
9 how often. There are a whole population now in the U.K. of
10 people who get up in the afternoon, start snorting ketamine and
11 carry on doing so until they crash out the next day and again.

12 So people who use recreationally, say, once or twice a
13 month are not having major problems, but those users who are
14 using heavily daily are having a huge amount of problems.
15 Brain imaging studies are showing fairly major changes. The
16 worst are their memory problems -- forget Ecstasy. These are
17 really, really large effects, very serious effects that you
18 would predict would really interfere with a person's
19 progression through school or college or in work.

20 And the most damaging effect of ketamine was actually
21 first discovered by a group in Boston where, if you use
22 heavily, it produces a new syndrome called ketamine induced
23 ulcerative cystitis where it actually produces ulcers on the
24 bladder. And in lots of young people, the bladders have had to
25 be removed. Some improve when they stop using daily. So

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1 long-terms of heavy ketamine use are really horrendous.

2 Q. Could you describe the effects briefly of marijuana or
3 cannabis?

4 A. Marijuana, cannabis is a very variable thing and contains a
5 lot of different things depending on where you are in the
6 world. But in general, it is well known that cannabis will
7 impair memory, both acutely and, to some extent, in the
8 long-term in a similar way to what we have been talking about
9 with people that use Ecstasy. But, clearly, cannabis, like
10 ketamine, used daily and heavily can produce a dependence that
11 is different from MDMA in that regard. And cannabis has other
12 harms if people are smoking joints because you get often not
13 only chemicals in marijuana, but it is often also rolled in
14 tobacco. You can get respiratory problems.

15 Q. How would you compare the harms of MDMA to the harms of
16 marijuana and ketamine?

17 A. MDMA is certainly not as harmful as ketamine for all of the
18 reasons I just outlined. MDMA and cannabis, well, MDMA doesn't
19 cause dependence where cannabis can, though most people use
20 cannabis recreationally not heavily. So probably they are
21 similar in terms of harm.

22 Q. Are there any studies supporting the conclusion that MDMA
23 is not more harmful than either of the other two drugs?

24 A. Well, there have been studies where they have used
25 something called multidimensional analysis to look at to try to

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1 get a way of comparing all drugs together or all illicit drugs.
2 I know there was a recent paper in The Lancet which is
3 the top medical journal showing a U.K. effort to do this where
4 they rated, using techniques that an American called Larry
5 Phillips used, and he is a behavioral economist who basically
6 provides his work for financial organizations and issues like
7 where to fight radioactive waste control. And they use this
8 multidimensional scaling to have a whole bunch of experts rate
9 20 drugs for, first of all, harms that each of those drugs do
10 to the individual; and, secondly, harms that it does to
11 society.

12 And on the scales of those 20 drugs in terms of harm
13 to the individual, Ecstasy is ranked 17th out of 20, so three
14 from the bottom, in terms of harm to the individual. The top
15 three, as you would predict, are heroin, crack cocaine and
16 methamphetamine.

17 In terms of harm to society it is even lower. It
18 ranks 18. So it is well below marijuana and ketamine and
19 cocaine -- well below that. It is also well below methadone
20 which is a major treatment for heroin addiction with which it
21 ranks equally with the marijuana equivalency tables.
22 Q. Do these result that you are just describing in The Lancet
23 study, are they confirmed?

24 I'm sorry. Let me start again.

25 Have any other papers reached similar conclusions?

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1 A. Yeah. I think recognizing this issue, it is similar in
2 lots of different countries. There is already one that has
3 been published by the Dutch where they used a similar approach
4 to also rank the 20 major illicit drugs in Holland. And the
5 similarity was amazing -- very, very similar. That is probably
6 reflecting the fact that U.K. and Holland have similar issues.
7 But it shows the validity of this kind of approach.

8 Q. Finally, since you have worked with all three substances --
9 marijuana, ketamine and MDMA -- do these results ranking MDMA
10 lower in terms of harmfulness than the other two conform to
11 your own experience?

12 A. Definitely, yes. Ketamine is a really nasty substance.

13 MR. MICHAELMAN: We have been through a lot of
14 technical material today, and as I wrap up, I would like to
15 make sure that I have your main points, with the Court's
16 permission to conduct a brief summary?

17 THE COURT: Go ahead.

18 BY MR. MICHAELMAN:

19 Q. I understand you to have testified that the state of the
20 field has changed quite a bit since 2001 and that many of the
21 other earlier studies were flawed?

22 A. Yes.

23 Q. I understand you to have testified that current research
24 shows that MDMA has little persistent effect outside of a small
25 cognitive impairment?

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1 A. Yes.

2 Q. I understand you to have testified that in the 2001 report
3 by the U.S. sentencing commission, the harms of MDMA were
4 overstated?

5 A. They probably reflect what was known at the time, but
6 looking back on them now, yes, they were overstated.

7 Q. And I heard you to testify that MDMA is less harmful than
8 ketamine?

9 A. Yes.

10 Q. And that MDMA is no more harmful than marijuana?

11 A. That's right too.

12 MR. MICHAELMAN: Thank you very much.

13 THE COURT: Let me suggest we take a 10-minute recess
14 and then, Mr. Chung, you will proceed with cross-examination.

15 MR. CHUNG: Of course, your Honor.

16 THE COURT: We will take 10 minutes.

17 Dr. Curran, you can step down.

18 Be back in 10 minutes.

19 (Recess)

20 THE COURT: Cross-examination.

21 MR. CHUNG: Yes.

22 THE COURT: Go ahead.

23 CROSS-EXAMINATION

24 BY MR. CHUNG:

25 Q. Good morning.

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0C6UMCC2 Curran - cross

1 A. Good morning.

2 Q. Professor Curran or Dr. Curran -- how would you like to be
3 addressed?

4 A. I don't mind.

5 Q. I will go with Dr. Curran.

6 Dr. Curran, you are the author of a 1997 paper
7 entitled "Mood and Cognitive Effects of MDMA, Weekend High
8 Followed by Mid Week Low," is that correct?

9 A. Yes.

10 Q. That was published in an academic journal called Addiction?

11 A. Yes.

12 Q. And that journal is what is commonly termed a peer review
13 journal?

14 A. Yes.

15 Q. So all of papers that are submitted and published in that
16 journal undergo review by a number of experts in the field?

17 A. Yes.

18 Q. In that study -- we are talking about the 1997 study -- you
19 indicated that recreational use of MDMA is widespread, is that
20 correct?

21 A. It would have been at the time, yes.

22 Q. So and the purpose of that study was to -- and I am quoting
23 from the article itself -- "examine both the acute and residual
24 effects of MDMA on users' mood and cognitive function," is that
25 correct?

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0C6UMCC2

Curran - cross

1 A. Yes.

2 Q. And a number of human subjects participated in that
3 subject, is that correct?

4 A. Yes.

5 Q. The first part of that study was to speak to those human
6 subjects at a dance club, correct?

7 A. Yes. Or to recruit them, yes.

8 Q. But you recruited them at a dance club, correct?

9 A. Yes. It was an unusual set-up because there had been very
10 little work on MDMA at that point. And I found a student who
11 came to me because he was a disc jockey in a rave in north
12 London and I saw the possibility that he could set up a
13 laboratory at the rave and take people off the dance floor, if
14 he wanted, to talk to us and be tested in a controlled way. So
15 that's what we did.

16 Q. Is it correct that approximately two dozen of those
17 individuals were recruited to participate in the study?

18 A. Yes. It was a small study. It was one of the first, yes.

19 Q. Now, a dozen of those individuals reported having taken
20 MDMA at the club, correct?

21 A. Yes.

22 Q. And then a dozen others reported having only consumed
23 alcohol at that club, correct?

24 A. Yes.

25 Q. You administered a number of tests on those two dozen or so

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0C6UMCC2 Curran - cross

1 subjects at the club, correct?

2 A. Yes.

3 Q. And those tests were designed to determine their mood?

4 A. Yes. We were looking at mood and cognitive function.

5 Q. You first administered those tests at the club in that
6 laboratory setting that you described?

7 A. Yes.

8 Q. Then you administered the test again the next day on those
9 same two dozen subjects?

10 A. Yes.

11 Q. And then you administered those tests again about three
12 days, again, on those same 24 individuals?

13 A. Yes.

14 Q. And you found that the MDMA users, the dozen or so MDMA
15 users had a significantly elevated mood at the club compared to
16 the alcohol only users, correct?

17 A. Yes.

18 Q. But significantly lower mood several days later?

19 A. Yes.

20 Q. The mood of some of those MDMA users several days later in
21 fact, you said, qualified as clinical depression, correct?

22 A. What we --

23 Q. Yes or no. I asked you the question. The mood of those --

24 A. Yes, yes.

25 THE COURT: Excuse me.

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0C6UMCC2 Curran - cross

1 Dr. Curran, on cross-examination, Mr. Chung is
2 entitled to ask leading questions that call for a yes or no
3 answer. If you can answer the question yes or no, please try
4 to do so. If you can't answer it yes or no, tell Mr. Chung
5 that and it will be up to him to decide how to proceed.

6 THE WITNESS: Thank you.

7 THE COURT: You are welcome.

8 BY MR. CHUNG:

9 Q. You also found that the MDMA users, again, the MDMA only
10 users, showed significant problems with paying attention,
11 correct?

12 A. I think the task was 07 -- which task are you talking
13 about?

14 Q. I am talking about just generally, upon administering the
15 battery of tests on the subjects, you found, according to your
16 study, that the individuals who only used MDMA had problems
17 with attention?

18 A. I call it working memory, but if you want to call it
19 attention, fine.

20 Q. Understood.

21 So there were problems with working memory with the
22 MDMA users?

23 A. Yes.

24 Q. You indicated that one of the possible mechanisms for your
25 finding was the depletion of serotonin in the MDMA users?

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0C6UMCC2 Curran - cross

- 1 A. Yes.
2 Q. You also indicated that another possible mechanism for your
3 finding was serotonin neurotoxicity, correct? I am just
4 talking about this 1997 study.
5 A. I don't know if I mentioned it there, but it is
6 conceivable, yes. It could have been that.
7 Q. Now, you were also the author of a paper entitled "Some
8 Acute Effects of MDMA on Mood, Evidence of Gender Differences,"
9 and that was published in 2002 in the journal entitled
10 Psychopharmacology. Do you recall that?
11 A. Yes.
12 Q. And that is another peer review journal?
13 A. Yes.
14 Q. In that published study, you indicated research with
15 animals suggested that serotonin function may be attenuated for
16 a period following a single dose of MDMA, correct?
17 A. Yes.
18 Q. Again, that same published study, you indicated that if the
19 same is true in humans, then functions sought to be modulated
20 by serotonin may differ in MDMA users compared with non-users a
21 few days after the drug is taken, correct?
22 A. Yes.
23 Q. And that mid week depression in female users was correlated
24 with the amount of MDMA taken, correct?
25 A. Yes.

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0C6UMCC2 Curran - cross

- 1 Q. And that MDMA users rated lower levels of aggression than
2 controls on the night of drug use, but significantly higher
3 levels of aggression mid week?
4 A. Yes.
5 Q. And that in males, change in aggression correlated with the
6 amount of MDMA taken on the weekend, correct?
7 A. Yes.
8 Q. And one of your conclusions was that women are more
9 susceptible than men to mid week low mood following weekend use
10 of MDMA, is that right?
11 A. Yes, in that paper.
12 Q. Another conclusion of that paper was that both men and
13 women show increased self-rated aggression upon taking MDMA,
14 right?
15 A. Yes. Questionnaire.
16 Q. You interpreted those results to come from an attenuation
17 of serotonin function for a period following acute use of MDMA?
18 A. Yes.
19 Q. In July 2001 -- and I know this was a long time ago -- you
20 attended a conference held by the U.S. International Institute
21 on Drug Abuse entitled "MDMA Ecstasy Research, Advances and
22 Challenges, Future Directions," correct?
23 A. Yes.
24 Q. That was at the National Institute of Health campus in
25 Maryland?

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0C6UMCC2 Curran - cross

- 1 A. Yes.
2 Q. You made a presentation at that conference?
3 A. Yes.
4 Q. In addition to many other researchers in the field of MDMA?
5 A. Yes.
6 Q. And Glen Hanson gave the opening remarks at that
7 conference?
8 A. Yes, he did.
9 Q. He was the director of the Drug Abuse Institute's division
10 of neuroscience and behavioral research at the time?
11 A. Glen Hanson?
12 Q. Yes.
13 A. He probably was. I can't remember.
14 Q. Minor detail.
15 You know Glen Hanson personally?
16 A. I have met him at conferences, but I don't know him very
17 well.
18 Q. Your presentation at that conference was about the effect
19 of MDMA on the body's ability to use tryptophan, is that right?
20 A. That was a study that I reported there, yeah.
21 Q. But that is a study that you reported at that conference?
22 A. And then published, yes.
23 Q. Tryptophan is an amino acid that plays a part in the
24 production of serotonin?
25 A. Yes.

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0C6UMCC2 Curran - cross

1 Q. It is more popularly known as what makes people sleepy when
2 they eat turkey, right?

3 A. That's news to me.

4 Q. I am just trying to provide some context here.

5 You had conducted research on the interaction between
6 on MDMA and this chemical tryptophan?

7 A. It was with MDMA users where we challenged them with either
8 enhanced tryptophan, the thing you need in your diet to make
9 serotonin or deplete it, so it was either MDMA users, current,
10 ex or non-users.

11 Q. Well, thank you for answering my next three or four
12 questions.

13 That research involved three groups of human subjects,
14 right?

15 A. Yes.

16 Q. One group was MDMA users, current users, right?

17 A. Yes.

18 Q. And the second group was individuals that had stopped using
19 MDMA for more than one year?

20 A. Yes.

21 Q. And, third, individuals that had never used MDMA?

22 A. Yes.

23 Q. And all of the study participants, as you had indicated
24 before, were given beverages or drinks that contained a large
25 amount of tryptophan?

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0C6UMCC2 Curran - cross

- 1 A. They were given drinks either containing a large amount of
2 tryptophan or no tryptophan. That was the manipulation.
3 Q. So both, they were provided with both drinks, a tryptophan
4 drink and a no-tryptophan drink, right?
5 A. Half of each group was given one of the treatments, so half
6 of each group would have been given a drink containing
7 tryptophan as well as all of the other essential amino acids we
8 need in our diet. The other group were given all the amino
9 acid we need in our diet except tryptophan.
10 Q. Five hours later after you gave them this variety of
11 drinks, you measured the level of tryptophan in the
12 participants' blood.
13 A. In the plasma, yes.
14 Q. Blood is same thing as plasma?
15 A. Yes, plasma is part of blood.
16 Q. You found that the ex-users of MDMA showed higher levels of
17 tryptophan in their blood than the non-users or current users?
18 A. We did, yes.
19 Q. At the conference, you stated tryptophan should cross the
20 blood-brain barrier to be incorporated in the biosynthesis of
21 serotonin but in ex-users significantly higher levels of
22 tryptophan remained in their blood, is that correct?
23 A. Yes.
24 Q. In other words, in these ex-MDMA users, the tryptophan was
25 not being metabolized at normal rates, is that right?

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0C6UMCC2 Curran - cross

1 A. It was being significantly less metabolized than the other
2 two groups.

3 Q. You also gave the subjects a number of memory related
4 tests?

5 A. Yes.

6 Q. Upon administering these tests, you found that the current
7 MDMA users did more poorly than did the non-MDMA users, is that
8 right?

9 A. I will take your word for it. I can't remember every
10 detail. I think that we found that the ex-users were the ones
11 who were impaired.

12 Q. This was your study, right?

13 A. Yes.

14 Q. The ex-users, like you said, did the poorest on the test?

15 A. Yes.

16

17 (Continued on next page)

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0C64MCC3 Curran - cross

1 BY MR. CHUNG:

2 Q. You stated at the conference that there is a clear
3 correlation between blood levels of tryptophan, a functional
4 deficit, and the total dosage and length of time these people
5 used MDMA before they stopped?

6 A. Yes.

7 Q. You are the author also of *Quitting Ecstasy*, an
8 investigation of why people stop taking the drug and their
9 subsequent mental health. That was published in the 2003 in
10 the *Journal of Psychopharmacology*?

11 A. Yes.

12 Q. Do you remember that paper?

13 A. Yes.

14 Q. The *Journal of Psychopharmacology*, like the other ones --

15 A. Peer review.

16 Q. Now in that paper you indicated the regular use of Ecstasy
17 has been associated with depressed mood, anxiety and hostility,
18 but it is not known whether such effects persist after people
19 stop using the drug, is that correct?

20 A. Yes.

21 Q. You indicated in that paper the aim of the present study
22 was to examine the reasons why ex-users had stopped using this
23 drug?

24 A. Yes.

25 Q. An another aim of the study was to assess these ex-users'

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OC64MCC3 Curran - cross

- 1 current level of depression, anxiety, anger, and aggression,
2 correct?
3 A. Yes.
4 Q. In that study you conducted telephone interviews with
5 individuals who used to take MDMA on a regular basis but who no
6 longer use the drug?
7 A. That's right, yes.
8 Q. The participants were made of up of 66 ex-users, correct?
9 A. Yes.
10 Q. These individuals used to take MDMA regularly but had not
11 taken MDMA for at least about a year?
12 A. Yes.
13 Q. Is it true that they have not taken MDMA for on average
14 about three years?
15 A. If my memory serves, yes.
16 Q. The participants were then asked about why they had quit
17 taking MDMA, right?
18 A. Yes.
19 Q. They also completed questionnaires to assess their mood?
20 A. Yes.
21 Q. You stated in that paper that the ex-users, the subjects in
22 your study, could be divided into two groups based on their
23 reason for quitting?
24 A. Yes.
25 Q. The first group were those who quit for mental health

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0C64MCC3 Curran - cross

1 reasons?

2 A. Yes.

3 Q. The second group were those who quit for what you call
4 circumstantial reasons?

5 A. Yes.

6 Q. Approximately half of those in that first mental health
7 group scored in the range for clinical depression?

8 A. Yes, in the mild zone.

9 Q. For clinical depression?

10 A. Yes.

11 Q. In that group, the levels of depression and anxiety
12 correlated significantly with the amount of MDMA that these
13 individuals had taken several years previously?

14 A. In the mental health group, yes.

15 Q. You stated in that paper that that finding suggested that
16 users may either be more vulnerable to the adverse effects of
17 MDMA or may have had preexisting mental health problems for
18 which they medicated by using, self-medicated by using Ecstasy?

19 A. Yes.

20 Q. So two possibilities you mentioned in that paper?

21 A. Yes.

22 Q. But you also concluded that a study showed that some
23 ex-users experienced an impairment to mental health that
24 persisted for years after they stopped using the drug, correct?

25 A. Yes. It would make sense to say that if it was a

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0C64MCC3 Curran - cross

1 preexisting problem.

2 Q. But that wasn't one of your conclusions, correct, that you
3 found among the individuals that participated in the study that
4 a number of them had mental health impairment years after they
5 had last used the drug?

6 A. Yes, OK.

7 Q. Dr. Curran, have you reviewed the expert summary, the
8 document of Glen Hanson that was prepared in advance of this
9 hearing?

10 A. I read it, yes.

11 Q. It was a 2-page document?

12 A. Yes.

13 Q. Did you review the publications that were cited in that
14 summary?

15 A. Yes, there was the Degenhardt paper.

16 Q. One of those papers was authored by a research group headed
17 by Fabrizio Schifano?

18 A. Yes.

19 Q. Are you familiar with Dr. Schifano?

20 A. Yes.

21 Q. You testified during direct examination that approximately
22 ten people in the U.K. per year die of Ecstasy-related causes?

23 A. That's right; that's exactly the statistic that's in the
24 Schifano paper.

25 Q. In the Schifano paper, isn't it correct that the study

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0C64MCC3 Curran - cross

1 found that from 1997 to 2007, approximately 605 people died as
2 a result of MDMA use?

3 A. No, it doesn't say that in that paper.

4 Q. It doesn't say that?

5 A. No.

6 Q. You testified on direct examination that 99.9 percent of
7 MDMA users use other types of drugs?

8 A. Yes.

9 Q. Many MDMA users use marijuana?

10 A. Yes.

11 Q. Many of them use cocaine?

12 A. Yes.

13 Q. Many of them use methamphetamine?

14 A. Methamphetamine is quite rare in the U.K.

15 Q. That's what we have been calling throughout this hearing
16 the polydrug use?

17 A. Yes.

18 Q. Polydrug use is what's commonly called a confounding factor
19 when it comes to the MDMA studies?

20 A. It's one of the confounding factors.

21 Q. It's a confounding factor that you believe subjects a
22 number of MDMA studies to criticism?

23 A. Yes.

24 Q. You agree that out in the field in real life, 99.9 percent
25 of MDMA users are polydrug users?

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OC64MCC3 Curran - cross

- 1 A. Yes.
2 Q. You are familiar with Andrew Parrott?
3 A. Yes.
4 Q. You are aware that he is, among other things, a professor
5 Swansea University in the U.K.?
6 A. Yes.
7 Q. You are aware that he has published over 46 peer review
8 articles regarding MDMA?
9 A. I never counted; I take your word for it.
10 Q. You discussed one of those papers during your examination,
11 right?
12 A. Yes.
13 Q. A 2001 paper entitled, a 2001 survey of literature
14 regarding MDMA?
15 A. It was a review, yes.
16 Q. It was published in the Journal of Human
17 Psychopharmacology?
18 A. Yes.
19 Q. That is a peer review journal?
20 A. Yes.
21 Q. It's a journal that you yourself have quoted in a number of
22 papers?
23 A. Over the years, a few.
24 Q. You consider Professor Parrott's, that 2001 paper
25 whimsical?

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0C64MCC3 Curran - cross

- 1 A. I was describing narrative reviews as being whimsical; I
2 wasn't being rude to Dr. Parrott. For the reasons I stated, a
3 narrative review can be quite biased.
- 4 Q. So all narrative reviews are whimsical?
- 5 A. I am not saying that. You have good and bad narrative
6 reviews and good and bad systematic reviews. You have to judge
7 each by the quality. But what I was saying if you are
8 reporting the studies that show impairment in memory in MDMA
9 users, then for balance you should also report the studies that
10 don't show an impairment.
- 11 Q. You mentioned during direct examination a researcher Thelma
12 Schilt?
- 13 A. Yes.
- 14 Q. She is, among other things, a professor at the University
15 of Amsterdam in the Netherlands?
- 16 A. Yes.
- 17 Q. You included one of her papers among the items that you
18 were principally going to rely on?
- 19 A. Yes.
- 20 Q. That was a paper entitled Cognition in Novice Ecstasy Users
21 with Minimal Exposure to Other Drugs?
- 22 A. Yes.
- 23 Q. That was a publication the peer review journal, Archives of
24 General Psychiatry?
- 25 A. Yes.

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OC64MCC3 Curran - cross

1 Q. Obviously you have reviewed that particular paper?

2 A. Yes.

3 Q. Are you aware that one of the conclusions of that paper was
4 that although the performance of the group of Ecstasy users
5 that were part of that study is still within the normal range,
6 that long-term negative consequences of MDMA users cannot be
7 excluded? Are you aware that that was one of her conclusions,
8 or one of the researchers' conclusions?

9 A. I don't remember exactly the discussion but I know the
10 result. The effect of a very well-designed study was that when
11 people, they didn't, the student groups didn't, before they
12 started using Ecstasy, one group started, the other didn't, and
13 when they were retested, the ones who had used Ecstasy recalled
14 half a word less than those who hadn't used Ecstasy.

15 But the discussion kind of did go on to conclude there
16 was a memory impairment. As I said before, half a word is like
17 saying you forgot one item on your shopping list of 30. It's
18 not relevant to your day-to-day functioning as a human being.

19 Q. You agree that this was I think you said a well-designed
20 study?

21 A. Yes, it was a well-designed study.

22 Q. But you don't remember whether one of the conclusions of
23 the Schilt group was that long-term negative consequences of
24 MDMA use cannot be excluded?

25 A. That doesn't mean anything.

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0C64MCC3 Curran - cross

- 1 Q. It doesn't mean anything?
2 A. Not really. If you say, it's best to go to the data, the
3 evidence. Conclusions can be something else. But the evidence
4 is in that very well-designed study by a very well-respected
5 group of researchers the actual effect was less than half a
6 word.
7 Q. You are also familiar with the researcher in the field
8 named Maartje de Win?
9 A. I don't know her; I am familiar with her work.
10 Q. Do you know she is also a professor at the University of
11 Amsterdam?
12 A. Yes. She is part of the group.
13 Q. She is part of the Schilt group?
14 A. The van den Brink group.
15 Q. She conducted numerous studies regarding MDMA, is that
16 right?
17 A. Yes.
18 Q. You already testified that you are familiar with Stephen
19 Kish, right?
20 A. Not personally; I know his very excellence paper in Brain.
21 Q. He is a professor of pharmacology at the University of
22 Toronto?
23 A. Yes.
24 Q. He has conducted a number of studies regarding MDMA?
25 A. Yes.

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0C64MCC3 Curran - cross

- 1 Q. Are you also aware, you don't have to be familiar with him,
2 a researcher named Brian Gallomodo?
3 A. The name rings a bell. Remind me of the paper.
4 Q. Professor and chair of the University of Toledo Medical
5 School Department of Neurosciences?
6 A. I don't.
7 Q. You are not aware of him?
8 A. Not that I can retrieve information now. I am happy to
9 look at the paper if you want me to look at it.
10 Q. You were asked a number of questions on direct examination,
11 about whether MDMA is addictive?
12 A. Yes.
13 Q. You said categorically, no, it's not addictive?
14 A. That's right.
15 Q. In the course of that discussion you mentioned an expert
16 named Cotler?
17 A. Linda Cotler.
18 Q. Are you aware or have you reviewed a paper by Cotler and
19 other authors entitled Ecstasy Abuse and Dependence Among
20 Adolescents and Young Adults, Applicability and Reliability of
21 the DSM-IV criteria?
22 A. I thing that's the Sidney/Miami study I mentioned earlier.
23 Q. That was published in the Journal of Human
24 Psychopharmacology?
25 A. OK. I don't know.

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OC64MCC3 Curran - cross

1 Q. That's the very same journal in which Professor Parrott's
2 2001 review was published?

3 A. Yes.

4 Q. In that study, the Cotler study, is it correct that the
5 research group conducted a survey of young adult and adolescent
6 MDMA users?

7 A. It wasn't a survey; I think it was an interview study.

8 Q. Interview study. These individuals, these young and
9 adolescent MDMA users were interviewed by the research group?

10 A. Yes. They had a computerized testing system and they
11 offered to people 55 pounds, \$55 to come and talk about their
12 use all kinds of drugs. These were polydrug users, I think 40
13 percent of whom used heroin. So they are not typical of
14 recreational Ecstasy users.

15 Q. Are you aware that a conclusion of that 2001 Cotler study
16 was that 43 percent of those who were reported Ecstasy use met
17 the accepted diagnostic criteria for dependence according to
18 the DSM-IV?

19 A. I am aware of that but it's nonsense.

20 Q. That's nonsense?

21 A. Yes, it's nonsense.

22 Q. Are you aware that those results are, that according to the
23 Cotler group, those results were consistent with similar
24 studies in other countries that suggested a high rate of MDMA
25 dependence among users, correct?

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0C64MCC3 Curran - cross

1 A. I don't think there are studies, quality studies showing
2 rates of dependence among MDMA users.

3 Q. You consider this study, this 2001 study nonsense?

4 A. I think the conclusions are nonsense. What they did was
5 pay lots of drug users to come along and talk about their drug
6 use in return for money and they filled in, they used the
7 DSM-IV criteria to look at dependence. But Linda Cotler
8 constructed her own scale of what she called withdrawal, and if
9 you look at her actual results, as I said before, all you need
10 for a DSM-V diagnosis of dependence, is to tick 3 boxes on a
11 whole list of questions, like, have you ever taken more than
12 you intended to, have you ever been in trouble with the police,
13 do you get tolerance, do you get withdrawal.

14 What Linda Cotler did, I am sure in the best hope, was
15 just construct a special withdrawal scale for MDMA. But as you
16 remember, we were talking before about the midweek effects.
17 What she put on this scale are the midweek effects of Ecstasy
18 that she put on, you know. If you are thinking about the
19 timeline that the judge wanted before, you know when people
20 take Ecstasy, they are then not going to sleep very well. They
21 can go 24 hours more without sleep. Ecstasy is not the type of
22 suppressant that is widely used in obesity.

23 There were lots of midweek effects like slight
24 increase in aggression, decrease in depression. These are
25 Cotler's withdrawal scale. Those items were all there. What

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0C64MCC3 Curran - cross

1 she is doing is picking up the few-days-after effects of
2 Ecstasy. It's not the withdrawal state you see in people who
3 use drugs in the clinics, people who use drugs every day and
4 then go cold turkey. And we all know what heroin and alcohol
5 do, that sort of thing. So Linda Cotler's work has been
6 criticized and I criticize it for that reason.

7 The data I accept, of course, but the conclusions
8 about dependency are not valid and they wouldn't be valid in a
9 couple of years' time anyway because the new DSM categorization
10 will take out many of those criteria. If you look at the
11 actual participants in those Cotler studies, on average, they
12 were using Ecstasy one to two times per month. It's nonsense
13 to talk about use of the drug one to two times a month and talk
14 about addiction. It's common sense. You don't need to be a
15 scientist.

16 Q. In your opinion, regular use of Ecstasy once or twice a
17 month is not additional dependence.

18 A. Absolutely not.

19 Q. Absolutely not?

20 A. Absolutely not.

21 Q. On direct examination you were asked a number of questions
22 about the 2001 report by the U.S. Sentencing Commission
23 regarding the Ecstasy guidelines?

24 A. Yes.

25 Q. You were asked a number of questions about a section in

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(212) 805-0300

0C64MCC3 Curran - cross

1 that report regarding the physical effects of MDMA, is that
2 correct?

3 A. The physical effects?

4 Q. The effects of MDMA, the harm?

5 A. The harm of MDMA, yes.

6 Q. I believe your words were that the commission, you believe
7 that the commission came up with assumptions regarding the
8 physical harms of MDMA?

9 A. I didn't say anything about assumptions.

10 Q. That was your testimony, wasn't it?

11 A. I didn't use the word assumption. I think what I said was
12 that the commission in 2001 was based on the limited evidence
13 that was available at that point, including very high toxic
14 doses of MDMA given to animals.

15 Q. You recognize that the commission, again from the report,
16 recognized that the potential toxicity to serotonin neurons
17 have been the subject of some disagreement?

18 A. Yes.

19 Q. So the commission acknowledged there was controversy
20 regarding the neurotoxicity of serotonin?

21 A. Yes.

22 Q. You also recognize that the commission in that report also
23 acknowledged that another point of controversy surrounding MDMA
24 research literature is whether the loss of serotonin sites or
25 serotonin and the corresponding impairment is permanent?

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0C64MCC3 Curran - cross

1 A. Yes.

2 Q. You acknowledge that the commission realized that there was
3 a controversy among scientists regarding the permanence or the
4 lack of serotonin impairment?

5 A. Yes. That was based on the study with monkeys showing
6 serotonin depletion of seven years.

7 Q. At the time in 2001 there was quite of a bit of controversy
8 regarding these potential or actual physical harms?

9 A. Yes, that was acknowledged.

10 MR. CHUNG: No further questions.

11 THE COURT: Redirect.

12 MR. CHUNG: Your Honor, I don't want to assume certain
13 things, it looks like Mr. Rorty is going to be conducting Dr.
14 Curran's redirect examination. Is that normal practice.

15 THE COURT: It's not normal. Generally, one counsel
16 conducts the examination of a witness, but do you have any
17 objection.

18 MR. CHUNG: I don't. It's a sentencing hearing.

19 THE COURT: Fine.

20 Mr. Rorty, you have license to conduct the redirect.

21 MR. RORTY: Thank you.

22 REDIRECT EXAMINATION

23 BY MR. RORTY:

24 Q. I am going to ask you about a number of studies that
25 Mr. Chung just asked you about. Why don't we go in the same

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(212) 805-0300

0C64MCC3 Curran - redirect

1 order he proceeded in. Let's discuss the 1997 study regarding
2 recreational use, particularly the weekend high followed by the
3 midweek low; do you recall that study?

4 A. Yes.

5 Q. I am sorry, I don't have the full name; can you give us the
6 title of that study?

7 A. Plus or minus, the last bit, I can't remember the first
8 bit, it was Weekend High Followed By Midweek Low.

9 Q. Mr. Chung asked you about your finding that survey users
10 when asked about their midweek low reported a condition which
11 was consistent with clinical depression; have I understood that
12 correctly?

13 A. It was in a very small number of people, mostly in the mild
14 range, but the most important thing is that it was transitory.
15 When we did subsequent studies to go further into the finding,
16 it was only on like day 3 that you find any change in mood at
17 all. By the following Saturday, nobody was depressed; it was
18 literally just a dip a few days after. Dr. Parrott's shown
19 exactly the same thing in a publication. It only lasts for 7
20 days, it's midweek day or two out of 7 days.

21 Q. To the extent that users experience symptoms consistent
22 with clinical depression, they experience them for a 2-to-3-day
23 period?

24 A. Yes.

25 Q. That's all your study showed?

SOUTHERN DISTRICT REPORTERS, P.C.
(212) 805-0300

OC64MCC3 Curran - redirect

1 A. Yes, but on average it's on a very low level of change in
2 mood.

3 Q. To the extent, what I understand you to say, to the extent
4 they were consistent with clinical depression, it was mild to
5 moderate clinical depression?

6 A. Yes.

7 Q. Mr. Chung drew your attention to the conclusions in your
8 study and indicated that it was his understanding that you
9 attributed these effects to, quote, neurotoxicity in that 1997
10 study.

11 A. My memory --

12 MR. CHUNG: Your Honor, objection; that's not a fair
13 characterization of the question and answer on
14 cross-examination.

15 THE COURT: Put a new question to the witness. I am
16 sustaining the objection as to form.

17 Q. Did your study conclude that the findings of clinical
18 depression were the result of the neurotoxic effects of MDMA?

19 A. The conclusion from that study was that either the dipping
20 mood midweek was due to serotonin depletion or to the fact that
21 if you have such a fantastic time, you feel so high and
22 euphoric on Saturday, then anything in comparison is less
23 appealing. But it also said serotonin neurotoxicity cannot be
24 ruled out based on what was known of the animal work in 1996
25 when I wrote that paper.

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0C64MCC3 Curran - redirect

1 Q. Your conclusion with respect to neurotoxicity was not a
2 finding of neurotoxicity --

3 A. Not at all.

4 Q. -- but the conclusion that it cannot be ruled out?

5 A. It can't be ruled out, but to explain both findings,
6 neurotoxicity wouldn't really help because it's only a
7 temporary depletion. Those findings fit much better with
8 animal and human evidence showing after you take Ecstasy on
9 Saturday night, your serotonin levels go whoosh and then up
10 again. I just take that whoosh low and then they are back to
11 normal the next Saturday. It's a transient effect.

12 Q. To clarify, temporary serotonin depletion is not the same
13 as neurotoxicity?

14 A. Not at all, no, it's kind of a normal function of the brain
15 in response to lots of drugs.

16 Q. If I understood the answer you just gave when you said that
17 neurotoxicity cannot be excluded, that was a reaction in part
18 to then-existing animal studies that through the administration
19 of high toxic doses claimed to find neurotoxicity?

20 A. Yes.

21 Q. Can you discuss the meaning of the inclusion of a phrase in
22 a study that a finding cannot be excluded? What do researchers
23 take from that? What does it mean to include that finding?

24 A. It's standard in science and research to try to consider
25 every possible explanation for what you found so every single

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(212) 805-0300

OC64MCC3 Curran - redirect

1 alternative should be there in a balanced discussion so that's
2 why all three explanations are talked about.

3 The toxicity wouldn't explain any dip midweek; that's
4 nothing to do with toxicity. It fits much better if it's shown
5 not only by Dr. Parrott but also by ourselves many times now,
6 this is just a temporary blip during the week following weekend
7 Ecstasy use. That can't be neurotoxicity; it has to be a
8 temporary serotonin depletion.

9 Q. The 2002 gender study, Mr. Chung drew your attention to
10 findings concerning aggression and a comparison between male
11 and female increased aggression. Did those findings relate to
12 short or long term effects of MDMA?

13 A. Again, they are exactly the same effect; it's that midweek
14 dip which we found repeatedly in 2002. It doesn't speak to
15 neurotoxicity; it just speaks to that temporary depletion.

16 Q. From your 2002 study, would you conclude or do you believe
17 a reasonable researcher could conclude that MDMA causes
18 longterm increase in aggression in either men or women?

19 A. No.

20 MR. CHUNG: Objection.

21 THE COURT: Sustained.

22 Q. Did you make any findings concerning longterm increases in
23 aggression in that 2002 study?

24 A. There are two types of measurements that are used about
25 individuals that are called trait measures which are enduring

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(212) 805-0300

0C64MCC3 Curran - redirect

1 features. Some people are more aggressive than others. We
2 measure those in ways like aggression questionnaire or we look
3 at corridors like testosterone or whatever else. Then there
4 are fluctuations that we all as human beings go through. So
5 even if we are not predisposed to be depressed or predisposed
6 to be aggressive, there might be times when you are stressed,
7 when you are very happy that your mood changes. Those are
8 called state measures.

9 In our studies of aggression there has been no
10 difference in trait measures between Ecstasy users and
11 nonusers. So the enduring features about those human beings
12 are not different. What changes are state aggression. They
13 are just a blip midweek again. That's the most consistent
14 finding.

15 MR. CHUNG: Your Honor, I am not sure the witness's
16 response was responsive to Mr. Rorty's question. I believe the
17 question was were there any findings with respect to longterm
18 effects from the 2002 study.

19 THE COURT: You can follow up on recross if you wish.

20 BY MR. RORTY:

21 Q. Let me move to the 2001 conference presentation regarding
22 tryptophan and the paper which followed. I understand that you
23 gave a presentation there but you later either just previously
24 or later published a paper summarizing that research. Before
25 we discuss the effect of tryptophan, I would like to clarify

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(212) 805-0300

OC64MCC3 Curran - redirect

1 something both Mr. Michelman and Mr. Chung touched on. Can you
2 further describe the difference between functional impairment
3 and brain damage?

4 A. Well, you can have brain damage, for example, if you have
5 been in terrible motorbike crash, the most common cause that I
6 know of, you actually got brain damage. Areas of the brain
7 have actually been killed off. The brain is plastic; other
8 areas may take over. But when you have severe brain damage and
9 cell death, that usually means that your day-to-day life is
10 impaired. If you have had damage to hippo campos, your daily
11 life will be hugely affected because your memory will be
12 severely impaired, and that would be specifically a permanent
13 effect.

14 If you are talking about a drug like MDMA, no one is
15 talking about cell death. There is no evidence that MDMA kills
16 braincells. But there is evidence of damage in the sense we
17 talked about before of the axons being shortened and regrowth
18 being abnormal. So, in that case, if you want to call that
19 brain damage, it doesn't have any functional effect. Even in
20 animals who are depleted of serotonin in the brain by 70 to 90
21 percent, they don't have memory problems. They just behave
22 completely normal. There are no functional consequences in
23 terms of their daily life. So brain damage in terms of
24 serotonin axons doesn't mean much if it doesn't affect that
25 human being's existence.

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0C64MCC3 Curran - redirect

1 Q. A change in the brain does not equate to functional
2 impairment?

3 A. Absolutely. Functional impairment is more important for a
4 human's life.

5 Q. In assessing harms which is of greater significance, brain
6 change or damage or functional impairment?

7 A. Functional impairment. Usually the two go together with
8 most forms of structural brain damage.

9 Q. Let's apply that to your tryptophan study. My
10 understanding was that you found that tryptophan is less
11 metabolized in ex-users of MDMA?

12 A. Yes.

13 Q. Is that a finding that equates to a functional impairment
14 in ex-users?

15 A. No.

16 Q. Explain.

17 A. It's purely, it's only functional impairment; it's just
18 reflecting blood levels of tryptophan which is a standard amino
19 acid that we all need from our daily diet. It doesn't mean
20 that every functional impairment --

21 Q. To go back to that distinction, your brain chemistry may
22 have temporarily or permanently changed, but it does not change
23 your ability to function in the world?

24 A. Absolutely, yes.

25 Q. Let's move to your 2003 study regarding quitting Ecstasy.

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0C64MCC3 Curran - redirect

1 You were asked questions about your conclusion that some
2 ex-users had impairment which persisted for years. What was
3 the impairment you were describing in that conclusion?
4 A. That was the study about mood.
5 Q. Would it help you to recall, it was a higher incidence of
6 subsequent depression?
7 A. In people giving up using Ecstasy.
8 Q. Yes, as opposed to people who had never used it.
9 A. Right. I am not sure what the question is.
10 Q. To the extent that you found that ex-users who had given up
11 MDMA had increased subsequent depression following MDMA use,
12 did your study correlate the MDMA use with the subsequent
13 depression? Do you believe there was a demonstrated
14 correlation between MDMA use and subsequent depression?
15 A. You are talking about the study where we looked at people
16 who had given up MDMA for different reasons?
17 Q. Yes.
18 A. I can't remember the size of the correlation, I am sure I
19 would have done it between Ecstasy use and depression. I have
20 to have look at the paper again to know the size of it and how
21 much variance that explained.
22 Q. I want to draw your attention to your discussion of the
23 potential confounding factors of preexisting mental health
24 conditions among those people who had increased depression
25 subsequent to Ecstasy use.

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OC64MCC3 Curran - redirect

1 A. Yes. I think that's important because in the early 2000s,
2 it was very difficult to find people in the U.K. who had given
3 up Ecstasy. In fact, we had to go onto a London TV station to
4 say what we are really looking for is people who are willing to
5 take part in our research who have given up Ecstasy. I think
6 that that way of sampling was not good because we obviously
7 attracted people who had more time, often they were unemployed,
8 and people who we think may have had more, a bigger
9 representation of people who had some kind of kind of mental
10 health problem that they were attributing to Ecstasy.

11 So, the confounds in that study are that you can't
12 rule out preexisting differences in depression, in anxiety. If
13 you think of not just my research, but of the research of Huizh
14 and of Leib and of other groups, and you put all that together,
15 it definitely now looks like the majority of people who
16 experience anxiety and depression after they have been using
17 Ecstasy, actually in these longitudinal studies where you can
18 look at children and their mental health status, they found 88
19 percent of Ecstasy users who had mental problems had those
20 problems in childhood.

21 Q. What does that tell you about your own 2003 study and its
22 conclusions?

23 A. Well, sure, the conclusions were that I couldn't rule out
24 preexisting differences and I couldn't say there was a causal
25 link between using Ecstasy and any anxiety or depression.

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OC64MCC3 Curran - redirect

1 Q. Let me turn to the Cotler study concerning dependence about
2 which Mr. Chung asked you?

3 A. Cotler.

4 Q. You discussed her own withdrawal criteria or metric.
5 Explain that. Did I understand that in addition to looking at
6 DSM criteria, she created her own metric for whether or not a
7 person was dependent and specifically whether they experienced
8 withdrawal?

9 A. Yes.

10 Q. Was that metric drawn from the DSM?

11 A. No. In the DSM there isn't, MDMA dependence does not
12 exist, there is nothing in the DSM about MDMA.

13 Q. Does the DSM contain criteria for dependence on other
14 drugs?

15 A. Yes.

16 Q. What other drugs?

17 A. Most of the abused drugs, heroin, crack cocaine, cocaine,
18 marijuana.

19 Q. So the authors of the DSM themselves drew a distinction
20 between MDMA and the drugs which have separate dependence
21 criteria?

22 MR. CHUNG: Objection.

23 THE COURT: Sustained as to form.

24 Q. Did the DSM authors draw distinction between MDMA and other
25 drugs in terms of designing criteria for dependence?

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(212) 805-0300

OC64MCC3 Curran - redirect

1 A. The DSM is only revised every so many years. In fact, at
2 the moment there is a big debate going on internationally about
3 how addiction is going to be diagnosed in the revision that's
4 due out in 2012. In fact, I mentioned before in that revision,
5 dependence is going out and they are going to bring back the
6 word addiction really. So, MDMA is not in the current DSM, but
7 checking with the future DSM, it's not even been considered for
8 inclusion in that. So I don't think your normal psychiatrist
9 working in the addiction field sees it as an entity at all
10 addictive.

11 Q. Let's move to your conclusion and discussion of the 2001
12 report. Mr. Chung asked you about the extent to which the
13 commission acknowledged that in 2001 there was a controversy
14 regarding neurotoxicity. Based on your earlier testimony and
15 your review of the decade of research since 2001, has that
16 controversy been resolved?

17 A. About neurotoxicity?

18 Q. Yes.

19 A. I think we are nearly there, but in terms of humans,
20 because as I mentioned before, most of the studies looking at
21 humans have shown that there is very focused, small change in
22 serotonin transporters while people are using Ecstasy, MDMA,
23 but the majority of the studies show when people have given up
24 or reduced, then that difference disappears.

25 MR. RORTY: Thank you. No further questions.

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(212) 805-0300

0C64MCC3 Curran - redirect

1 THE COURT: Any re-cross, Mr. Chung.

2 MR. CHUNG: No, your Honor.

3 THE COURT: I have a few questions.

4 Following up on this neurotoxicity question, putting
5 aside the now discredited studies by the court, are there not
6 other studies that indicate the neurotoxic effects of MDMA?

7 THE WITNESS: If you take changes in the axons in
8 animal brains, then lots of other studies show that there are
9 axonal changes if you give sufficiently high doses. I think
10 the key thing really is if you, I mean, as I said before, those
11 are really high doses, a bit like giving a bottle of bourbon a
12 day to a 2-year-old then concluding about the effects of
13 alcohol in normal social use.

14 The better monkey studies particularly by Fantegrossi
15 and Banks where the monkeys self-administered, first of all,
16 unlike other addictive drugs, over the 18 months, the monkeys
17 could self-administer, they self-administered less over time,
18 whereas addiction is the opposite; they actually
19 self-administer more. But more importantly in both those
20 studies where monkeys self-administered, there is absolutely no
21 change in the brain.

22 So more and more it's looking like those early
23 pre-2001 studies giving huge massive doses and the studies done
24 since then, some studies even used 20 to 40 milligrams a
25 kilogram in monkeys, of course, you are going to get toxicity

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0C64MCC3

1 by those counts, but wherever they have tried to model more the
2 pattern in which humans take Ecstasy, then there has been no
3 change at all in serotonin in the brains of monkeys.

4 THE COURT: Would it be fair to say that there is an
5 ongoing debate about the neurotoxicity of MDMA.

6 THE WITNESS: Science never stops in a sense, but I
7 think, you know, I talk a lot to colleagues in Holland and in
8 other places, and I think there is an emerging consensus now
9 that the early studies really make people worry, and looking
10 back on the evidence that's been gathered in the last decade,
11 we now have a much more balanced view. On the whole, if you
12 look at the quality studies published in high-quality journals
13 and the high-quality meetings that you can go to, there is an
14 emerging consensus. At least the top persons definitely agree
15 from the van den Brink people in Amsterdam who have done all
16 those recent NextC work, multimillion pound projects, I think
17 we would all agree that the 2001 report was based on available
18 evidence at the time. What we know now is that the exaggerated
19 fares that were coming from the cohort-based kind of studies,
20 McCann studies were far greater and don't translate to a normal
21 human Ecstasy user.

22 Does that answer your question?

23 THE COURT: Yes.

24 You have noted in your testimony that MDMA is not
25 addictive.

SOUTHERN DISTRICT REPORTERS, P.C.
(212) 805-0300

0C64MCC3

1 THE WITNESS: Yes.

2 THE COURT: But didn't the National Institute on Drug
3 Abuse, didn't they come up with a conclusion that something
4 like 43 percent of Ecstasy users, I think I can quote, met the
5 accepted diagnostic criteria for dependence as evidenced by
6 continued use despite knowledge of physical or psychological
7 harm, withdrawal effects and tolerance, close quote. I would
8 like you to respond to that.

9 THE WITNESS: That's exactly the study I was talking
10 about. If you go into the NIDA website, that's exactly what
11 you see, 43 percent meet criteria. This is in the Linda Cotler
12 study we were talking about that was done in Sydney and Miami.
13 But that is nonsense because the people in that study, there
14 were several hundred, the average use of Ecstasy was once or
15 twice a month. I was trying to say before that when you are
16 dealing with addiction, you don't talk about addiction in terms
17 of use of a drug once or twice a month. It's not what the
18 concept means in terms of common sense, let alone science.

19 What that study was showing was that if you take the
20 boxes, Linda Cotler had this DSM criteria, the boxes that were
21 ticked for those criteria, she only needed 3, were first of all
22 tolerance, which is true, like with most drugs, people either
23 increase the dose of Ecstasy they take over time or they
24 experience less effect if they keep on the same dose. That's
25 absolutely true; tolerance you see.

SOUTHERN DISTRICT REPORTERS, P.C.
(212) 805-0300

0C64MCC3

1 What the problem was withdrawal because she created
2 her own scale of withdrawal where the measures were the same as
3 what happend the night or a few days after taking Ecstasy. One
4 interesting thing about the same study is she went back both in
5 Sydney and Miami to the same people to see if she got the same
6 effects a week later, to see if it was a reliable instrument,
7 and it wasn't reliable in one respect. People changed their
8 responses and they changed their responses particularly on this
9 withdrawal scale because the main reason for changing responses
10 was they didn't understand what the question was.

11 So the user had thought about withdrawal as being the
12 aftereffect, whereas withdrawal, when you are talking about in
13 the addiction field, withdrawal is more like the cold turkey
14 you get with heroin or something else. There has never been an
15 MDMA withdrawal syndrome described. I think the Cotler studies
16 have been funded by NIDA and so NIDA always publicizes their
17 own work on that site, but categorically I don't believe that
18 people taking a drug once or twice a month have an addiction
19 problem.

20 THE COURT: At least twice in your testimony you
21 referred to the mortality rate from MDMA to be ten deaths per
22 year in Great Britain.

23 THE WITNESS: Ten deaths a year due to Ecstasy.

24 THE COURT: On cross, Mr. Chung asked you about the
25 Schifano study and he asked you whether the Schifano study

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(212) 805-0300

0C64MCC3

1 reported that there were 605 Ecstasy-related deaths between
2 1997 and 2007 and you said in substance, no, the report doesn't
3 say that. I would like you to clarify this matter because I
4 can show you where the report does say that.

5 THE WITNESS: Yes. There is a difference between the
6 number of deaths that are due to Ecstasy and the number of
7 deaths that are Ecstasy-related where Ecstasy had been put on
8 the death certificate. If you look at that Schifano paper,
9 there are, I think he had two data sources. One is a very good
10 data source in the U.K., kind of a national data source whereby
11 instead of just going on what it says on the death certificate
12 where Ecstasy could have been listed alongside heroin or other
13 drugs so that would have been counted as Ecstasy-related death,
14 whereas the death was probably due to respiratory depression
15 because of heroin. That's where that figure comes from is that
16 data set.

17 There is a much better data set which Schifano goes on
18 to talk about which is a data set where all coroners in the
19 U.K. have to send in a detailed report so that it's not just
20 these drugs were found in the blood system or in the tissue of
21 people who were dead after drug or any other kind of incident,
22 but a detailed report by a coroner on every single drug-related
23 death in the U.K. It's a much more reliable database because
24 lots of people with drugs die of lots of different kinds of
25 drugs.

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0C64MCC3

1 The figures I was quoting are figures for the ten
2 cases per year, deaths due to Ecstasy are known to be due to
3 Ecstasy, hypothermia and hyponatremia. In that paper I can
4 show you Schifano has the same thing. He's talking about over
5 the same period of years. I just divided that by the number of
6 years. So Schifano's paper is exactly commensurate with
7 Rogers' paper reviewing deaths. They both have ten per year
8 caused by Ecstasy rather than just Ecstasy being one of the
9 drugs in the system. Does that make it clear.

10 THE COURT: It does. Thank you.

11 You rely fairly heavily on the David Nutts studies
12 which attempt to characterize the harmfulness of several
13 illicit drugs based on a survey of experts. In his articles he
14 uses a term that I just love that I would only attribute to the
15 Court of Appeals, Delphic analysis. Can you tell me whether
16 you think that that's really the appropriate type of a study
17 for this court to take into account.

18 THE WITNESS: I agree with you; I am a bit skeptical
19 about Delphic analysis. The paper I was talking about was the
20 2000 paper where he has given up Delphic analysis. He is using
21 Larry Phillips who is a very prestigious American professor in
22 economics. He is using his multicriteria division analysis
23 which is a lot less wobbly than Delphic. It sounds like Greek
24 myth, doesn't it.

25 THE COURT: For example, the study Development of a
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 (212) 805-0300

0C64MCC3

1 Rational Scale to Assess the Harm of drugs of Potential Misuse.

2 THE WITNESS: That was the Delphic one.

3 THE COURT: Yes.

4 THE WITNESS: That wasn't the one I suggested.

5 THE COURT: Then would you agree that the Delphic
6 analysis can't appropriately take the place of scientific data
7 on the harms of Ecstasy?

8 THE WITNESS: I think the Delphic analysis was a first
9 attempt then got a lot of coverage and other scientists came in
10 and said there is a much better way of doing this and that's
11 what resulted in the more recent paper.

12 THE COURT: Thank you.

13 Now, do counsel wish to make any further inquiries of
14 Dr. Curran based on the court's inquiries. Anything from the
15 defendants.

16 MR. RORTY: Yes, just one question.

17 REDIRECT EXAMINATION

18 BY MR. RORTY:

19 Q. The court just asked you about the Nutts studies. I
20 thought I heard you say that you referred to a paper in which
21 Dr. Nutts abandoned the Delphic analysis in favor of this far
22 more reliable analysis. You said that the good paper, the post
23 Delphic analysis paper was 2000. That's what you just said.

24 A. 2010.

25 Q. So, the more recent study, in fact, the study this year in

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(212) 805-0300

OC64MCC3 Curran - redirect

1 which Dr. Nutts ranks drugs, can you say again for
2 clarification where MDMA is ranked in that study, the 2010
3 study which abandoned the Delphic analysis for a more reliable
4 analysis?

5 A. Yes. In the reliable analysis, Ecstasy in terms of harm to
6 self ranked 17th at the bottom out of 20; in terms of harm to
7 society, 18th out of 20.

8 THE COURT: Mr. Chung.

9 MR. CHUNG: Just a couple.

10 THE COURT: We will try to finish this. Typically we
11 break for lunch at 1:00. We will finish Dr. Curran, then we
12 will break.

13 RE CROSS EXAMINATION

14 BY MR. CHUNG:

15 Q. The court asked you a series of questions about your take
16 on whether there is a debate about the neurotoxicity of MDMA;
17 do you remember those questions?

18 A. Yes.

19 Q. You answered some questions about studies that were relied
20 upon by the Sentencing Commission in 2001, right?

21 A. Yes.

22 Q. I want to take you back to something you testified about, a
23 study you testified about initially on direct examination by
24 Mr. Michelman about a study on authored by Stephen Kish and a
25 research group at the University of Toronto. You stated that

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0C64MCC3 Curran - recross

1 was an excellent study?

2 A. Yes. It controlled many more factors than previous
3 studies.

4 Q. That was a study published in a journal entitled Brain?

5 A. Yes.

6 Q. That's a peer review journal?

7 A. Yes.

8 Q. You have had a chance to review that paper?

9 A. Yes.

10 Q. That paper, among other things, examined the effects on
11 users of MDMA who had used low dosages or what are commonly
12 termed recreational dosages?

13 A. Yes.

14 Q. Isn't it correct that you one of the conclusion, I
15 understand that it's a conclusion not the evidence as you
16 distinguished already, that the low dosages of MDMA might cause
17 damage to neurons that are involved in the generation of
18 serotonin, correct?

19 A. If he said neurons he means serotonin transporters because
20 that's what we looked at.

21 (Continued on next page)

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1 Q. I am quoting from the paper itself again, Steven Kish, 2010
2 paper?

3 A. Yes. He did a PET study so he was looking at serotonin
4 transporters.

5 Q. "The suggestion that more distal targets of brain stem
6 serotonergic neurons, including the occipital cortex, might be
7 more susceptible to potential toxic damage from Ecstasy is
8 supported by some limited non-human primate data showing that
9 the cerebral, especially the occipital cortex, is more
10 vulnerable to Ecstasy than striatum in terms of the persistence
11 of serotonin reduction."

12 Do you remember that passage from the article? I know
13 that it was a long --

14 A. To be honest, no.

15 Q. But upon hearing that, is it fair to say that one of the
16 conclusions or one of the suggestions from the Kish study is
17 that low dose Ecstasy can have toxic effects or toxic damage on
18 serotonin generating neurons in the cerebral cortex?

19 A. Not really. Kish actually says that, unlike the earlier
20 studies, pre-2001, his study shows there is no global changes
21 in the brain, that they are very much specified to two areas he
22 showed, the hippocampus --

23 Q. My question is focused on those specific areas of the
24 brain. I agree with you. I tend to agree with you that he
25 doesn't speak to global change in the brain --

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0C6UMCC4 Curran - cross

- 1 A. No, very specific changes.
2 Q. And to what specific areas of the brain?
3 A. Specific to the hippocampus and occipital cortex.
4 Q. And the occipital cortex is part of the cerebral cortex of
5 the brain?
6 A. Yes.
7 Q. And is it correct that the cerebral cortex makes up the
8 lion's share of the brain?
9 A. Yes, the --
10 Q. About 90 percent?
11 A. In what terms?
12 Q. Just in terms of the size of the brain?
13 A. The cerebral cortex is kind of a convoluted area. If you
14 rolled out your cerebral cortex, it would be like a huge
15 tablecloth going from back all around there.
16 Q. I doubt it will be that large.
17 A. I am sure it will. And it is the thickness and whatever
18 the count and the folds what differentiates humans from
19 animals' brains. It is the cerebral cortex that folds in and
20 out much more, so we have a much greater area. If you roll out
21 a rat brain, you are talking about a postage stamp.
22 Q. It is a large part of the brain, right?
23 A. Yeah.
24 Q. Just in terms of volume?
25 A. Yeah. I don't know how much it weighs compared to the

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0C6UMCC4 Curran - cross

1 other bits, but the most important part of the cerebral cortex,
2 if you are looking cross-species is that our foreheads come
3 forward, whereas monkeys tend to go back. And these are the
4 latest of the evolved bit of the cortex response for executive
5 functioning and for higher level intelligence in the human
6 beings. But the occipital back there isn't as important, but I
7 think --

8 Q. OK. Just a couple of questions about the 2010 Nutt
9 study --

10 A. Yes.

11 Q. Now, you had a chance to review the paper that was
12 generated in the Lancet Journal as a result of Nutt's exercise
13 in that study?

14 A. The 2010 paper, yes.

15 Q. Reading directly from that Lancet publication, are you
16 aware that the method employed by the participants in that
17 study was -- I am reading directly from the publication --
18 "members of the Independent Scientific Committee on drugs,
19 including two invited specialists met, in a one-day interactive
20 workshop to score 20 drugs on 16 criteria." Were you aware of
21 that?

22 A. Yes.

23 Q. By the way, were you one of the participants?

24 A. No. I was not around at the time, but I am a member of
25 that committee.

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0C6UMCC4 Curran - cross

1 Q. So you recognize that they sat down for one day and then
2 came up with the analysis?

3 A. Yes. They had previously developed the criteria.

4 Q. But in terms of analyzing the drugs against this
5 multi-criteria decision analysis, they took one day to do it?

6 A. It took a lot longer with the advisory council, misuse of
7 drugs, to formulate the criteria on which drugs should be
8 evaluated and --

9 Q. My question was --

10 A. In terms of application you are right. Larry Phillips came
11 along and gave a whole day, and people completed the task in
12 eight hours, yes.

13 Q. Eight hours?

14 A. I wasn't there, but I presume it was about that -- eight to
15 ten hours.

16 MR. CHUNG: Thank you.

17 No further questions.

18 THE COURT: Anything further, counsel?

19 MR. MICHAELMAN: No thank you.

20 THE COURT: With this 2010 article, the 2010 Nutt
21 study, is it your view that it is appropriate to survey experts
22 as is done in the Nutt 2010 study in lieu of collecting
23 objective evidence?

24 THE WITNESS: It is very hard. There is no perfect
25 way of comparing 20 illicit drugs. So the way they decided to

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0C6UMCC4 Curran - cross

1 start was to bring in experts from all different viewpoints of
2 different drugs and experts who had a wide range of experience,
3 so it just wasn't someone who knew the heroin world or
4 whatever, but it was people who had a broad understanding.

5 I'm sorry. What was the question again?

6 THE COURT: That study is another survey of experts?

7 THE WITNESS: Yes.

8 THE COURT: In that sense, it is not so different from
9 the Delphic analysis that you were talking about before, is it?

10 THE WITNESS: Well, I think it is because it is a much
11 more objective method. And the Dutch people who did the same
12 thing, the same expert committees came up with pretty much the
13 same thing. We also did an Internet study of 1500 users and
14 asked for their view on the same criteria. And they came up
15 with pretty much the same thing as well.

16 So there is no perfect way of doing it. The marijuana
17 equivalence is a way of saying the drugs are ranked like this
18 as well. There is objective data used where you can, for
19 example, in the multi-criteria decision-making, you are using
20 objective index called the lethal dose of a drug, so we know
21 that that is defined as the ratio of a normal dose of a drug to
22 the lethal, so that is a number. So wherever there is
23 objective data -- and we have lethal dose on every drug because
24 that is required by all sorts of government bodies -- so for
25 lethal dose, that is a completely objective part of that and

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1 that was fed directly in. So where there is objective
2 evidence, it is fed directly in, but there is going to be
3 something of a value judgment between experts about things that
4 we don't have objective evidence on.

5 There is no study comparing all 20 drugs in one
6 population that could be meaningfully done. And so the next
7 best way of doing it is to get experts to rate, to see if users
8 also rate it the same, see if different countries come up with
9 a similar kind of framework. I don't know what would happen if
10 we compared it to the marijuana equivalency, there might be
11 differences, but different countries have different drug
12 problems, so you would need to have it reflect things that
13 changed over time.

14 THE COURT: The sentencing commission in its report to
15 Congress compared cocaine and MDMA. It said cocaine was a
16 stimulant but MDMA was both a stimulant and a hallucinogen. Do
17 you have a comment on that observation by the Sentencing
18 Commission to Congress?

19 THE WITNESS: Yes. They are both stimulants. The
20 reason that they put that in 2001 that MDMA was also a
21 hallucinogen was that if you look at the structure of the
22 molecule, it has some similarities to mescaline, I think. But
23 in terms of its effects, there have been a few recent studies
24 where they have given MDMA in the laboratory to healthy people
25 and the hallucinogenic qualities are not really classic

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0C6UMCC4 Curran - cross

1 hallucinogenic. They are not like LSD. They were a
2 heightening of sensitivity to light and sound and color.

3 So it is not hallucinogenic, it is more of a
4 perceptual kind of enhancement. You don't see things when you
5 are on MDMA that are not there, unlike all of the other
6 hallucinogens. Also, hallucinogens as a class are not
7 addictive. So in comparison with cocaine, I think Ecstasy is
8 more of a stimulant like cocaine. That's why some people want
9 to call it an entactogen or an empathogen, to separate it out
10 as unique class.

11 It also concluded that cocaine -- I mean, if I was
12 comparing MDMA with cocaine, I would be more worried about
13 cocaine addiction which is an issue among some people.

14 THE COURT: All right. Thank you, Doctor.
15 Any further inquiries?

16 MR. RORTY: One follow-up to the Court's question
17 regarding the commission's characterization of MDMA as a
18 stimulant and a hallucinogen. In assessing harm, if something
19 has both -- let's accept for the moment that MDMA is a
20 hallucinogen. I understand your answer, but I am going to ask
21 you to assume for purposes of this question that it has
22 hallucinogenic properties. Does the fact that one drug fits in
23 two categories make it inherently more harmful or is it doubly
24 harmful because it has two kinds of effects?

25 THE WITNESS: I can't imagine why. Alcohol is a
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1 stimulant in small doses and a depressant in others. I don't
2 know that is relevant, really, to thinking about it.
3 MR. RORTY: Thank you.
4 THE COURT: Anything further, Mr. Chung?
5 MR. CHUNG: No, thank you.
6 THE COURT: Dr. Curran, you are excused as a witness.
7 You may step down.
8 (Witness excused)
9 THE COURT: We will take our luncheon recess.
10 We will reconvene at 2:30.
11 (Luncheon recess)
12
13 (Continued next page)

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A F T E R N O O N S E S S I O N

2:30 p.m.

THE COURT: Is Dr. Halpern going to be the next witness?

MR. MICHAELMAN: Yes.

THE COURT: This Court has had an opportunity to review the memorandum submitted by defendant McCarthy.

Does either side wish to be heard further before the Court rules?

MR. RORTY: Yes, your Honor, briefly.

I would ask the Court to recognize a couple of aspects about this motion. The relevant impeachment in this case should, at most, include the two alleged false statements by Dr. Halpern and exclude those collateral matters that do not go to credibility and are not relevant to this hearing.

I think that because of Dr. Halpern's status as an expert witness and the nature of this inquiry, the relevant scope of impeachment is very different than it would be for a fact witness in this case. The false statements go to credibility. We understand they will be admitted and Dr. Halpern will answer questions about that. The remaining information, I do not believe can possibly serve to impeach his scientific findings. Because he is testifying to scientific opinions, he is in a very different position than a fact witness at trial or, indeed, at sentencing.

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1 In support of our position, although, of course it
2 does not have precedential value, I think it is relevant to the
3 Court's decision that the government took exactly the same
4 course in a fairly recent case in which Dr. Halpern testified
5 in the District of Oregon. As here, on the eve of
6 Dr. Halpern's testimony, the government made a virtually
7 identical proffer.

8 Judge Owen Panner in the District of Oregon excluded
9 not only the conduct to which we object, the substance of the
10 grand jury investigation, but also the false statements
11 themselves. We are concerned, as I know we all are, with the
12 Court's time and the efficiency of this hearing. You have
13 allocated a limited time. And consider in balancing the
14 prejudicial effect and the probative value and judicial
15 efficiency, I think that all of those considerations add up to
16 the exclusion of the extrinsic evidence of the collateral
17 matter concerning Dr. Halpern's status as a grand jury witness
18 and his role in that investigation, but permitting Mr. Chung --
19 and we don't disagree -- to impeach Dr. Halpern with two
20 alleged false statements.

21 THE COURT: Anything from the government, Mr. Chung?

22 MR. CHUNG: A brief response, your Honor.

23 I think that, first of all, the underlying conduct
24 that was in our factual proffer is part and parcel of the false
25 statements that were made by Dr. Halpern to government agents.

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0C6UMCC4b

1 And, really, the underlying conduct itself speaks to
2 Dr. Halpern's credibility as an expert witness. They go to his
3 bias. They go to his background, how his previous research
4 efforts in hallucinogenics were funded, from what sources and
5 what part he played in obtaining those funding sources.

6 Now, our case here, our proceeding here is worlds
7 apart from the District of Oregon case where Dr. Halpern
8 testified. That case was about a religious group that was
9 seeking an exemption from the Controlled Substances Act to be
10 able to use a particular hallucinogen as part of their
11 religious practices. Dr. Halpern was one among several
12 witnesses in that case, and the issue in that case was whether
13 that religious group could use that substance under the -- I
14 believe it is the Religious Freedom Restoration Act. In Judge
15 Panter's decision, there was no opinion or reasoning, at least
16 on the record, offered for his decision.

17 In this proceeding here, the purpose of the proceeding
18 is to figure out or at least to inform the Court about the
19 physical effects of MDMA and perhaps, more squarely, the state
20 of the scientific debate about physical effects of MDMA. Your
21 Honor is going to hear from four witnesses. They all have
22 published studies about MDMA. They all have their conclusions
23 or their opinions about the scientific debate. Just because a
24 witness is an expert does not mean he or she is immune from
25 credibility issues. And where the credibility issues go

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1 straight to why or are probative of why the witness takes a
2 certain position, we believe that evidence is admissible as
3 impeachment.

4 MR. RORTY: One further comment, if I may, in response
5 to Mr. Chung's point. He indicated, I believe, that he
6 believes that the evidence is relevant in part because it goes
7 to the funding for Dr. Halpern's research. The proffer does
8 not allege that Dr. Halpern took money from a person involved
9 in drug activity and used it for his research. It is
10 completely attenuated from that. What it says is that he took
11 money from a foundation. And it alleges that he knew that that
12 foundation had received money from a person involved in drug
13 trafficking.

14 And I would proffer that Dr. Halpern's testimony would
15 be that he did not use any of the money which he received from
16 Mr. Carr, the individual described in the investigation, to
17 fund any of his research.

18 I would also note that, just in terms of taking up the
19 Court's time on a collateral matter, on Friday we requested
20 that documentary evidence which the government would use to
21 substantiate this proffer, Mr. Chung declined to provide any of
22 that evidence. And in the event that we go into this matter, I
23 am very concerned that we would have the right, either during
24 or subsequent to cross-examination, to review those materials
25 and then we might have to ask for a recess in order to prepare

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1 to address what I think is an extremely attenuated issue in
2 this case.

3 THE COURT: Counsel, Federal Rules of Evidence 608(b)
4 provides, in pertinent part, that specific instances of the
5 conduct of a witness may in the discretion of the Court, if
6 probative of truthfulness or untruthfulness be inquired into on
7 cross-examination of the witness concerning the witness's
8 character for truthfulness or untruthfulness.

9 "Misconduct involving violations of the narcotics laws
10 is not an act involving dishonesty or untruthfulness and,
11 therefore, may not be inquired into under Rule 608(b)." And I
12 am quoting the Eighth Circuit in United States v. Turner, 104
13 F.3d 217, 223, and also relying on United States v. Williams,
14 822 F.2d 512, 517 (Fifth Circuit 1987).

15 Here, the specific acts that the government seeks to
16 introduce involve alleged violations of the narcotics laws and
17 do not concern Dr. Halpern's character for truthfulness or
18 untruthfulness. However, the government is permitted to
19 inquire into the alleged false statements made by Dr. Halpern
20 in response to an inquiry by the government.

21 In the end, credibility is always an issue and,
22 therefore, we are not going to get into the collateral matters,
23 but on the truthfulness or lack of truthfulness of statements
24 made to the government, the government can inquire on
25 cross-examination.

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1 MR. CHUNG: Your Honor, may I ask just a brief
2 question?

3 There are two basic areas of criminal activity that we
4 proffered were committed by Dr. Halpern. There were
5 violations, involvement in LSD trafficking and there was
6 laundering of LSD trafficking proceeds which, according to our
7 proffer, Dr. Halpern accepted through research institutes to
8 fund his own research efforts and facilitated to fund other
9 research efforts. As the Court is aware, our position is that
10 that background, that past criminal activity with respect to
11 money laundering, goes to the heart of Dr. Halpern's
12 credibility, specifically, his bias.

13 I just wanted a clarification from the Court as to
14 whether the Court's ruling with regard to a controlled
15 Substance Act violation also applies to the money laundering
16 activity.

17 THE COURT: It does. We want to move forward on the
18 merits of what this hearing is about. I will let you challenge
19 him on his credibility, but I don't want to hear evidence about
20 what went on with alleged money laundering by the doctor. I
21 think you can ask him how his research is funded. If you want
22 to, you can explore that area. But when we get there, I will
23 rule if you pose a question that is objected to. All right.

24 MR. CHUNG: Understood.

25 THE COURT: Will the defendants call Dr. Halpern?

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0C6UMCC4b

1 MR. MICHAELMAN: Yes.

2 JOHN HAIM HALPERN,

3 called as a witness by the defendants,

4 having been duly sworn, testified as follows:

5 DIRECT EXAMINATION

6 BY MR. MICHAELMAN:

7 Q. Good afternoon, Dr. Halpern.

8 A. Good afternoon.

9 Q. Could you state your current position or positions, please?

10 A. Yes. I am the director of the Laboratory for Integrative

11 Psychiatry at McLean Hospital and associate psychiatrist at

12 McLean Hospital and assistant professor of psychiatry at

13 Harvard Medical School.

14 Q. What are your main job responsibilities in those roles?

15 A. My main job responsibilities include furthering the

16 research goals of my laboratory which is on the effects of

17 hallucinogens in man, as well as the training of medical

18 students and residents and postoperative fellows and providing

19 clinical psychiatry services within the hospital, as well as

20 private practice.

21 Q. Could you share any other professional associations or

22 activities?

23 A. I am a member of the American College of Psychiatrists, and

24 I am board certified in general psychiatry and recently

25 recertified.

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0C6UMCC4b Halpern - direct

1 Q. What degrees do you hold?

2 A. I hold my bachelor degree in biological sciences from the
3 University of Chicago, and my medical degree from the State
4 University of New York.

5 Q. Could you please describe your area of research expertise?

6 A. My area of research expertise is the use and abuse of
7 hallucinogens and the way in which they are used in a culture.
8 It is mostly focused on the impact of this drug use in humans.

9 Q. Where do you get the funding for your study?

10 A. Over the years, the largest amount of money that has come
11 to me has been from the National Institutes of Health and,
12 specifically, the National Institute on Drug Abuse. I have
13 also received money from some foundations and from some private
14 donors.

15 Q. As the Court is aware, we submitted a draft that is about
16 to be published of one of your papers for the Court's
17 consideration in this case. Where did you receive funding for
18 that study?

19 A. That study was funded from the National Institute on Drug
20 Abuse for five years, actually, when Dr. Hanson was national
21 director of NIDA.

22 THE COURT: What is the title of that study, if it has
23 a title at this point?

24 THE WITNESS: It is on long-term neurocognitive
25 consequences of Ecstasy abuse.

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0C6UMCC4b Halpern - direct

1 THE COURT: Thank you.

2 BY MR. MICHAELMAN:

3 Q. Have you been retained as an expert witness before?

4 A. I have.

5 Q. Can you describe by whom and in what types of cases?

6 A. Certainly.

7 I was retained in a capital murder trial in Florida as
8 an expert witness in which the defendant's use of LSD played
9 prominently in that trial.

10 I was retained in a family court matter of a divorce
11 case in which one parent is a native American who follows the
12 ways of the native American church and wanted to let his son
13 participate in a peyote ceremony and the divorced mother did
14 not. I filed an amicus curiae brief in a matter that went to
15 the Supreme Court.

16 I was also an expert witness in a case that was just
17 mentioned, the Church of the Holy Light of the Queen v. the
18 Department of Justice that was heard in Judge Panner's
19 courtroom in Oregon.

20 And I think in approximately 2006 I was retained by
21 the Department of Justice in a criminal case in the Eastern
22 District of New York.

23 Q. So I have heard you have received a great deal of funding
24 from the federal government. You have been retained as an
25 expert by the federal government. Have you done any other

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0C6UMCC4b Halpern - direct

1 expert work for the federal government?

2 A. Yes. I have participated in several workshops for the
3 National Institute on Drug Abuse, twice in one of the work
4 groups that votes on providing grants from the National
5 Institutes of Health, and I have also participated in some
6 development projects for native American researchers that was
7 earlier this year.

8 Q. When did you begin your work in MDMA?

9 A. Separate from my training and clinical experience and
10 dealing with people who struggle with substance abuse in terms
11 of research, approximately eight years ago.

12 Q. What types of studies have you done?

13 A. So I have spent five years doing a research study looking
14 at the long-term neurocognitive consequences of Ecstasy, from
15 recruiting within a very specific population of all night dance
16 party goers, some of whom use only Ecstasy -- or almost only
17 Ecstasy -- versus people who actually don't use any drugs at
18 all. That is my NIDA-funded study.

19 And then I have another study in which we are
20 furnishing MDMA in the study as MDMA-assisted psychotherapy as
21 a research tool for dying cancer patients. So I am the
22 principal investigator of that study and I am not actually
23 administering the MDMA myself.

24 Q. Has all of your work been with human subjects, or do you
25 work with animals as well?

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0C6UMCC4b Halpern - direct

1 A. All of my work has been with human subjects.

2 Q. Can you describe the work you have done involving cocaine
3 during your career?

4 A. Yes. I, again, in addition to my work as a practicing
5 clinical psychiatrist, I administered cocaine source from NIDA
6 looking at the effects of cocaine on the endocrine system and
7 for acute immune response to the exposure to cocaine.

8 Q. For the record, once again, NIDA is the National Institute
9 on Drug Abuse that you referenced earlier?

10 A. That's correct.

11 Q. Dr. Halpern, as you just heard from the argument and the
12 judge's ruling, the government has sought to put before the
13 Court allegations that you lied to the government on two
14 different occasions, one in connection with your application
15 for certification as a Schedule I researcher and second in a
16 proffer session as a cooperating witness. And I would like to
17 ask you about each of those briefly.

18 Could you explain the circumstances of the incident
19 regarding the Schedule I certification?

20 A. Yes. I had testified in the grand jury and was instructed
21 by my lawyer to never disclose that I had participated in the
22 proceedings of a grand jury where I might reveal anything that
23 was spoken in there, if it is in a public setting. Sadly, when
24 the field investigators for my Schedule I application asked
25 this -- basically went to this question, it was in a public

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0C6UMCC4b Halpern - direct

1 setting and I denied and I regret that. I had thought that it
2 would have been clarified up in a private interview, but that
3 didn't happen.

4 Q. So just to clarify, the field investigators were government
5 field investigators?

6 A. They were field investigators of the DEA. I was told that
7 I should assume that they are aware of this matter and that
8 they may ask about it.

9 Q. And who told you that you should assume their awareness?

10 A. My lawyer.

11 Q. Then they asked you about your involvement in the
12 investigation and you denied it on the advice of counsel?

13 A. That's correct.

14 Q. You said this occurred in a public setting. Can you tell
15 us who else was present when the question was asked?

16 A. It was asked in the middle of a very busy pharmacy of a
17 hospital, so there are lots of people walking by in a public
18 place. It was not sitting down in a private office, me and the
19 investigators.

20 Q. Did the study for which you were seeing the Schedule I
21 certification ultimately go forward?

22 A. Yes.

23 Q. Did it go forward with you as principal investigator?

24 A. Yes.

25 Q. But not with you as the Schedule I registrant?

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(212) 805-0300

0C6UMCC4b Halpern - direct

1 A. That's correct.

2 Q. Can you explain how that came to be?

3 A. In this matter, the DEA is not required to -- there is no
4 deadline of response, and this is a study with dying cancer
5 patients. And while we are waiting to get some answer from the
6 DEA, I even had a couple of potential participants in the study
7 die, so months were going by. So it was recommended to me
8 actually from the DEA office that handles Schedule I
9 registrations that things would move faster if I had one of my
10 colleagues on my treatment team instead apply. And so rather
11 than wait further for an answer, whether it will be approval or
12 an order to show cause, I withdrew my application and one of my
13 colleagues applied and another set of interviews happened and
14 then it was approved.

15 Q. And his application still named you as the principal
16 investigator?

17 A. Yes.

18 Q. And it was granted?

19 A. Yes.

20 Q. Since that incident, the federal government has retained
21 you as an expert witness?

22 A. Yes. To the best of my recollection, I believe that the
23 Eastern District of New York hired me after that incident, yes.

24 Q. So you are not quite sure about this?

25 A. Not quite sure at the time.

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0C6UMCC4b Halpern - direct

1 Q. Fair enough.

2 Since that incident, the federal government, through
3 NIDA, the National Institute on Drug Abuse, has continued to
4 fund your work on MDMA?

5 A. It did.

6 Q. With regard to the second issue, the proffer sessions as a
7 cooperating witness in an investigation, can you describe the
8 circumstances in which the government has alleged that you were
9 dishonest?

10 A. Yes. It is an extremely scary position to be in. I had
11 the very foolish notion of leaving out information about my
12 childhood best friend, the full extent of my childhood best
13 friend's involvement in that investigation, and so I was not
14 truthful in those earlier -- in those first initial proffer
15 sessions. But I completely regret doing that, and I did make
16 it right and rectified what I had failed to do as originally
17 promised to them. So full disclosure of everything eventually
18 did occur.

19 Q. And it was, again, after that event that you were retained
20 as an expert witness and continued to be funded by NIDA, is
21 that correct?

22 A. Yes, that's correct.

23 Q. Thank you, Dr. Halpern.

24 THE COURT: Mr. Michaelman, before you move into a
25 substantive area, and I sense you are done with this area of

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1 inquiry at the moment.

2 MR. MICHAELMAN: I am.

3 THE COURT: We are going to take a very short recess
4 because I have the privilege of having the chief judge from the
5 bankruptcy court in Chicago in my courtroom, and I am going to
6 say hello to him for a couple of moments.

7 We will take five minutes.

8 (Recess)

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10 (Continued on next page)

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1 THE COURT: Mr. Michelman, you may proceed.

2 MR. MICHELMAN: Thank you, your Honor.

3 BY MR. MICHELMAN:

4 Q. So moving to the substance of the focus of the hearing on
5 the harms of MDMA, as I did with Dr. Curran, I would like to
6 ask you to state in summary for the court your conclusions on
7 the main topics we have asked you here to discuss today. Those
8 are the evolution of the field, the harmfulness of MDMA, and
9 the 2001 report. So, taking those in order, could you give us
10 your summary conclusion about the evolution of the field of
11 research into MDMA over the past decade.

12 A. Since the 2001 report, a tremendous amount of work,
13 research has occurred. That has given us much more information
14 than was available back in 2001. So, yes, that information now
15 informs us that would identify that 2001 report as being out of
16 date and excessively harsh in its conclusions.

17 Q. Just tick off briefly the ways in which you think the field
18 has changed since 2001.

19 A. I can think of globally about five different areas in which
20 things have improved since then. We know, we have much more
21 specific and accurate imaging techniques than the type of neuro
22 imaging studies than that occurred back at the time of that
23 report. We have much more data about cognitive function in
24 users and former users. We have information on types of biases
25 that can occur in subjects themselves, so-called stereotypic

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0C64MCC5 Halpern - direct

1 threat. People may believe they have been harmed when in
2 objective data they have not.

3 We have data on knowing that the estimation of dose in
4 animal models was quite excessive back over a decade ago. That
5 has been changed in more recent research. Finally, we now have
6 data on close to 400 human subjects now that have been
7 administered MDMA in clinical research.

8 Q. Finally, give us your summary conclusion about the
9 harmfulness of MDMA in general, what the current scientific
10 research shows.

11 A. MDMA can be quite harmful, it is by no means a benign drug,
12 but the risk for harm is modest at best. So a tremendous
13 amount of data in the interim has shown it not to be the type
14 of severely damaging and destructive drug as either described
15 or predicted back in 2001.

16 Q. Let's go into each of these areas in more detail. To take
17 the changes in the field of research first, you said the field
18 has changed in five ways. I would like to walk you through
19 each of these. Let's start with brain imaging. How has the
20 field changed with regard to improvements in brain imaging
21 technology.

22 A. The type of compound that's used to identify the serotonin
23 transporter, the way the serotonin is released from neurons in
24 the brain has become much more specific than originally used.
25 The compounds that were used back then are not used anymore.

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1 That's one of the important ways that it's changed.

2 Q. By back then you mean in 2001?

3 A. That's correct.

4 Q. So today, in a brain imaging study we might see things more
5 clearly than we would have a decade ago?

6 A. That's exactly what I mean.

7 Q. If I could take you then to the issue of what you call the
8 stereotypic threat which I believe you said was a bias in users
9 to report more harm than can be verified scientifically. Can
10 you talk about what we learned in that area?

11 A. There are a few different ways this may occur. If you put
12 on an advertisement saying we are going to do a study looking
13 at the harms from Ecstasy, you may get people selecting
14 themselves for volunteering because they have this belief that
15 of course they have been harmed. That may not be reflective of
16 what their real performance is.

17 In fact, we have seen research done showing that some
18 MDMA users will say that they have memory problems, but then
19 when we objectively test them on this, the types of memory
20 problems they have, we don't realize this. I am referring to
21 the work by Dr. Gillander Bettie and Dr. Harriet Dewitt at the
22 University of Chicago. Dr. Bettie's PhD dissertation in fact
23 was on this.

24 Q. If we could turn now to the area of cognitive impairment,
25 you had mentioned that had changed as well. What types of

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1 problems were believed to exist with respect to MDMA and
2 cognitive impairment 10 years ago.

3 A. Quite pointedly, much research was focusing in on verbal
4 memory deficits. That was the phrase that was most commonly
5 encountered back then. So, what we have learned since that
6 time is that some of the verbal memory deficits are actually
7 related to associated mental health problems. People who have
8 psychiatric illnesses like depression and anxiety and
9 untreated, their cognitive performance will be impaired.

10 Earlier studies did a very poor job of controlling for
11 mental illness, but there are other problems with the research
12 design back then. We heard a lot earlier this morning about
13 the use of confounds, the methodological flaws in the studies.
14 There are numerous ones when it comes to the evaluation of
15 cognitive performance of MDMA users.

16 Q. Could you list some of those?

17 A. Some of those types of confounds include an inadequate time
18 from last use of drugs to the time of testing or inadequate
19 control for sleep. Some studies would have these people
20 recruited from all-night raves, frequently partying through the
21 night, we know that sleep impairment or lack of sleep will
22 degrade performance then a comparison group of college kids who
23 are sleeping well or there is no use of drug testing. There
24 wasn't even hair testing used or available back then that we
25 now can employ or the use of screening of the urine from

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1 metabolites in MDMA to control for even immediate recent use of
2 MDMA before testing.

3 There were quite importantly the majority of those
4 studies were done with very small numbers of people and so the
5 statistical power, the strength of the findings were impaired
6 by having small numbers of people getting a large battery of
7 tests. And also quite concerningly was this strategy of
8 employing polydrug users who didn't use Ecstasy versus polydrug
9 users who did use Ecstasy. Then we are supposed to assume that
10 this complex blending of drug use can be dealt with in this way
11 by comparing polydrug users, ones who have taken Ecstasy and
12 the other group that has not.

13 Q. Let me follow up on a couple of specific instances. You
14 mentioned the use of hair and urine testing. I infer from what
15 you said that you were referring to researcher's ability to
16 verify the subject had or had not taken the drug within the
17 time they were supposed to have?

18 A. That's correct.

19 Q. With regard to the polydrug use, you mentioned that the way
20 of controlling for that in the past was have a polydrug Ecstasy
21 user group and a polydrug non-Ecstasy user group. Today are
22 there are groups that compare Ecstasy users who don't use any
23 other drugs with people who don't use any drugs at all?

24 A. There have been a few. Dr. Curran mentioned a couple of
25 them, and in addition there is my own NIDA-funded research that

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0C64MCC5 Halpern - direct

1 specifically sought out relatively pure Ecstasy users for
2 enrollment.

3 Q. Then in general, you now named a number of factors that
4 were not adequately controlled for 10 years ago, would you now
5 say that those factors are better controlled in more and more
6 recent studies?

7 A. Yes.

8 Q. Moving on to dose, could you explain how the scientific
9 understanding of the appropriate dose to use in MDMA studies
10 has changed?

11 A. It's now believed that in animal studies, a comparable
12 human dose by bodyweight should be used in these animal studies
13 of approximately 1 to 2 milligrams MDMA per kilogram
14 bodyweight. When you look at animal studies, for example,
15 where that dosage is used, we do not find these same results as
16 were achieved in these earlier studies with doses that's were
17 40 times greater than that.

18 Q. You also mentioned the administration of MDMA to subjects
19 in clinical trials. Could you elaborate on that.

20 A. There have been a variety of studies in which MDMA has been
21 directly administered to human subjects. I believe roughly now
22 about 400 humans have been administered it. All of that any
23 reported serious adverse events or worse in those participants.
24 On top of this in the last year, there is a study published in
25 which MDMA was used experimentally for post traumatic stress

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1 disorder reporting positive results. And there is my study
2 also in which MDMA is administered to human subjects, so far
3 also no serious adverse events or reportable adverse events
4 have occurred.

5 Q. These have all been FDA-approved studies where they have
6 been in the United States?

7 A. Yes.

8 Q. Have they all been in the United States or some in other
9 countries as well?

10 A. Some occurred in other countries as well.

11 Q. What's the difference between a neurological change and a
12 functional consequence, a distinction we heard discussed in the
13 earlier testimony?

14 A. We have neurological changes throughout the life cycle and
15 certainly after medicines are administered that go into our
16 brains, for example. But just because there is a change
17 doesn't mean, brain change does not automatically translate to
18 brain damage. So, when we take a medicine that affects the
19 brain, the function consequence can overall be desirable, but
20 there can be side effects as we know, as I know as a physician,
21 some of which are not desirable. So, both the good results and
22 the bad results are both functional consequences of taking a
23 substance.

24 Q. When you try to assess the harm of a drug are you looking
25 at whether there has been a change in the brain chemistry

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1 primarily or whether there are deleterious functional
2 consequences?

3 A. This may come from my focus as a physician. I am looking
4 in terms of clinical health what are the consequences
5 functionally in this person's daily life, in their emotional
6 life, in their work life. That's where the greatest traction
7 is in discussing claimed benefits versus potential harms,
8 particularly if I am working with somebody who has a history of
9 drug dependence and trying to help them evaluate what their
10 drug use is doing to them.

11 Q. So, in light of all these changes in the field that you
12 have discussed, what does the recent literature show us about
13 the harms of MDMA?

14 A. The recent literature does identify harms from MDMA use,
15 even death when taken in an excessive amount. That being said,
16 for the vast majority of people who wind up taking Ecstasy,
17 MDMA, illegally the harms appear to be quite modest and
18 time-limited.

19 Q. Tell us about your own recent paper and what you found,
20 actually, first, your methodology and then your conclusion.

21 A. So, we have done the study twice. We published in 2006 our
22 pilot data on some 40 individuals, two groups of individuals
23 all recruited from the same all-night dance scene. One group
24 doesn't use Ecstasy or any other drugs. The other group has
25 focused only on using Ecstasy and has had little or no exposure

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1 to other drugs including tobacco and alcohol.

2 That deals with the issue I mentioned earlier trying
3 to compare these polydrug users, how about we try to avoid it
4 completely. The methods of this earlier pilot study and the
5 later larger one which is the impress manuscript is exactly the
6 same. We also insist on at least 14 days from last drug use at
7 time of neurological testing. Subjects provide a hair sample
8 so we test back for the last 3 months for drug use, including
9 specifically for MDMA. We do a Breathalyzer to make sure they
10 are not doing cognitive testing while there is any alcohol in
11 their system.

12 We collect a urine sample to make sure there is no
13 MDMA metabolites since it won't show up in the hair if they
14 just took it in the prior three days. That's the purpose of
15 getting the urine test. We also do spot tests for other drugs
16 of abuse at time of neurological testing. We also tested for
17 very carefully on issues of depression and anxiety, a very
18 comprehensive battery of psychiatric evaluation structured and
19 semi-structured in interview form, a neurological exam
20 performed on all individuals.

21 These were some of the refinements to this work that
22 address a number of the confounds that had been existing in the
23 prior literature. Of course, we are publishing on a much more
24 robust number of individuals too.

25 Q. What did your work conclude?

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1 A. When you look at comparing the MDMA users overall versus
2 the nonusers, on all of the cognitive tests there are no
3 statistically significant differences. When we split the group
4 of users into two groups, moderate users who have used MDMA 20
5 up to 55 times and heavier users who have used MDMA more than
6 55 times in their life, and we compare this to the nonusers,
7 again the moderate users, no differences. On the heavy users,
8 there are only a few measures, some statistically significant,
9 decreases in performance, but they are still globally
10 functioning in the normal range of cognitive performance.

11 I might also add that some of those tests there is
12 overlap in some of these cognitive tests. Were it to signify
13 something more ominous, these other tests measures that did not
14 even show statistical significance should, and they didn't.

15 Q. Are there some studies out there in the field that have
16 shown that MDMA does cause significant harm even after 2001?

17 A. Yes.

18 Q. Does the existence of those studies suggest to you that the
19 overall state of the field is in doubt or that the evidence is
20 equivocal about the harms of MDMA?

21 A. These studies, I think it's important to try to collect
22 them together, take a look at what can we learn from looking at
23 all of these studies in comparison. So we heard a little bit
24 about this from Dr. Curran this morning. I also cited
25 Dr. Rogers' 2009 paper, his comprehensive meta-analysis of

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1 research on the harms from MDMA, and those conclusions overall
2 show that the deficits are rather mild or modest in nature. I
3 agree with that assessment.

4 Q. If I understand you correctly, you are not saying that
5 there is no debate in the field about precisely what it does,
6 but when the field is viewed as a whole, there is definitely a
7 trend towards the view that the --

8 MR. CHUNG: Objection; leading.

9 THE COURT: Sustained as to form.

10 Q. Are you suggesting that all of the debates regarding the
11 effects of MDMA are settled?

12 A. I am not. MDMA, I think when we are looking at the type of
13 extreme damage that was described or predicted back in the 2001
14 U.S. sentencing report to Congress, that there is a fairly
15 strong consensus of opinion that those types of damages are not
16 being realized in the population of users, but there is still
17 ample debate when it comes to where the significance or where
18 we will find these kinds of mild to modest changes. But over
19 the big picture stuff that there is going to be this horrible
20 type of damage, we have got another decade of data that has
21 just failed to realize those types of predictions.

22 Q. You said a minute ago that some of the early predictions
23 had not been realized in terms of what has been seen in the
24 population. What do you base that conclusion on?

25 A. If we look at, for example, public health measures that

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1 survey for drug use or emergency room visits, for example, the
2 drug abuse warning network which surveys emergency room visits,
3 we are looking at maybe 15,000 emergency room visits in which
4 MDMA played a role in the last year or two per year in the
5 United States versus I believe 500,000 for cocaine.

6 When we look at the national household survey of drug
7 use put out by the Substance Abuse and Mental Health Services
8 Administration, we find that the numbers of people that have
9 been using cocaine, the number of people that have been using
10 MDMA, again there is this huge gap. Much more people using
11 cocaine

12 Q. Does the fact that more people are using cocaine suggest
13 that the emergency room visits that have been documented might
14 be proportional.

15 A. No, they are not proportional. It's a much greater
16 percentage of people using cocaine are resulting in emergency
17 room visits than the number of people that are using MDMA that
18 result in emergency room visits for MDMA.

19 Q. So to make sure I understand this right, more people use
20 cocaine?

21 A. Yes.

22 Q. And a higher percentage of those people end up in the ER
23 because of that?

24 A. That's right, in comparison to MDMA, yes. Sorry for the
25 awkward explanation.

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1 Q. Let's move on to discuss the 2001 report. Are you familiar
2 with the 2001 MDMA report to Congress by the U.S. Sentencing
3 Commission?

4 A. I am.

5 Q. How did you become familiar with the report?

6 A. I have a vague recollection of reading it way back when it
7 was issued and of course I reviewed it with great care in
8 preparation for this case furnished from you.

9 Q. One of the report's main conclusions is that MDMA is more
10 harmful than cocaine. Is that correct?

11 A. No.

12 Q. Why not?

13 A. Cocaine, especially as I have seen from my own clinical
14 experience, this last year, I helped run a partial program for
15 substance abusers in early recovery, people with mental health
16 problems and substance abuse coming to a day program
17 intensively to focus on their substance problems. For a whole
18 year I ran a team doing this. I can't even count how many
19 people I had to work with who had primary cocaine problems, but
20 I can tell you not one of them had a primary Ecstasy problem.

21 In talking with colleagues and residents' experience,
22 it's quite comparable. With MDMA, we don't find people
23 reporting to emergency rooms and to psychiatric practices
24 seeking treatment for MDMA abuse or theoretical MDMA
25 dependence, but we do with cocaine.

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1 Q. What types of problems would you see in the cocaine users?

2 A. Well, cocaine users after many years of abuse and heavy
3 use, run the risk of heart attack, of stroke, of death from
4 that, and many other problems, problems relating to having poor
5 nutrition, their mental health and physical health. We can do
6 a standard CAT scan of the brain that can show evidence of
7 strokes in the brain from their repeated longstanding cocaine
8 use. But I have never seen any imaging of an MDMA abuser
9 showing a lesion in the brain attributable to MDMA. I don't
10 know of any publications that show that either.

11 Q. Then on both measures that we have discussed today, both in
12 terms of the neurological changes in the brain and functional
13 consequences, would you say that cocaine is more harmful than
14 MDMA?

15 A. Yes.

16 MR. CHUNG: Objection.

17 THE COURT: Sustained but next question.

18 Try not to lead the witness.

19 MR. MICHELMAN: I understand.

20 Q. The report says that MDMA compares unfavorably to cocaine
21 because whereas cocaine is a stimulant, MDMA is both a
22 stimulant and a hallucinogen. In your opinion is that a
23 scientifically sound way to compare the two drugs?

24 A. When I read that statement in the sentencing report, it
25 really made me scratch my head. It almost read like this was

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1 supposed to be some sort of arithmetic; cocaine gets a score of
2 one, it's a stimulant and then MDMA gets a score of two because
3 it's a stimulant and a hallucinogen, one plus one equals two.
4 No, that's not using good science.

5 Q. Let's return to the types of harms we talked about,
6 neurological changes and functional consequences. Does the
7 fact of being a stimulant and a hallucinogen mean MDMA has
8 greater functional consequences for the user than cocaine?

9 MR. CHUNG: Objection.

10 THE COURT: Overruled.

11 A. No. Merely stating descriptive adjectives to a substance
12 does not by and of itself offer objective proof of danger.

13 Q. Does the fact that MDMA is a stimulant and a hallucinogen
14 mean that it is likely to have greater neurological
15 consequences for the brain than cocaine?

16 A. No, it does not.

17 Q. The report also claims that MDMA is neurotoxic. What do
18 you infer the report means by that term?

19 A. It was my impression that it meant that axonal death or
20 destruction of a portion of the nerve, of nerve cells.

21 Q. By this definition from what we know today is MDMA
22 neurotoxic?

23 A. No.

24 Q. Explain why not, how we know that.

25 A. If we give lethal or near lethal doses of MDMA to animals,

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1 you will see damage to the brain, but when you give doses in
2 the range of typical human use, animal studies of 1 to 2
3 milligrams per kilogram bodyweight mentioned earlier, these
4 sorts of changes are not realized. That's a very critical
5 point. In using human dosing we don't see this type of harm.
6 In fact, we see no differences in these imaging studies and
7 amount of serotonin transporters in the brain. We see, when we
8 do find it, we find recovery. On top of it, these sorts of
9 brain changes are known to occur in a number of medications
10 that have been FDA-approved, such as SSRI antidepressants, for
11 example.

12 Q. You discussed the importance of getting the dose ratio
13 right. For the court's benefit, I know among the studies
14 submitted to the court, I believe there was one that, I
15 shouldn't lead you, for the court's benefit, were any of the
16 studies submitted to the court ones that dealt with the
17 appropriate dosing level in MDMA studies?

18 MR. CHUNG: Objection; appropriate dosage level.

19 MR. MICHELMAN: I suggest witness is an expert and can
20 speak --

21 THE COURT: Overruled. We can drill down on it
22 depending on what his answer is.

23 A. Could you repeat the question, I apologize.

24 Q. Do you recall if any of the studies that were submitted to
25 the court addressed the issue of appropriate dosing levels in

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1 MDMA studies?

2 A. Yes. The Baumann paper from 2007, I believe focused in
3 very clearly about this issue of 1 to 2 milligrams per kilogram
4 bodyweight versus much higher doses administered, and doses of
5 1 to 2 milligrams per kilogram specifically stating that the
6 type of harms or evidence of neurotoxicity were not realized.

7 Q. Why was 1 to 2 milligrams per kilogram an appropriate dose
8 according to Professor Baumann?

9 A. Because that is approximately the dosage range that most
10 humans consume MDMA.

11 Q. The 2001 report was also concerned with changes to the
12 serotonin system. Serotonin is something we have heard a lot
13 about today. Can you give your view on whether the report's
14 concerns about the serotonin system have been borne out by the
15 scientific research that has occurred since 2001?

16 A. Yes. What was predicted back then, this concern that the
17 serotonin system would be permanently damaged, there were
18 public health messages including that maybe people would no
19 longer respond to antidepressant treatment because of this, or
20 there would be a whole generation of people that will be
21 afflicted with depression because of damage to their serotonin
22 system. None of this has been realized in the intervening
23 years, either from direct research, public health surveys, or
24 from my own clinical practice and observation.

25 Q. Let's talk about some of the other risks in the report.

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1 The report is concerned that MDMA raises the heart rate, is
2 that correct?

3 A. Yes, MDMA will raise heart rate. So will coffee; caffeine
4 will do that too.

5 Q. The report is concerned that MDMA induces, quote, a strong
6 urge to repeat use, unquote. Is that finding justified?

7 A. That finding is absolutely not justified. Their own
8 reference to support that contention was referring to a website
9 www.heroin.org which they themselves in the footnote refer to
10 as offering a compendium of science, pseudoscience and lore,
11 quote unquote. That's the only reference they offered for that
12 contention.

13 Q. The report itself cited this website and described it that
14 way?

15 A. That's right.

16 Q. The related question that was the subject of some
17 discussion earlier, is MDMA addictive?

18 A. In the classical sense of addiction, no. There may be
19 periods of compulsive use. The vast majority of users do not
20 become physiologically dependent or drug-seeking and go into a
21 lifestyle of drug use and that alters their life forever like
22 we find with cocaine or heroin dependence or alcoholism for
23 that matter.

24 Q. The report sites concerns about fatalities; do fatalities
25 occur as a result of MDMA use?

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1 A. Yes, fatalities have occurred sadly, but it appears if you
2 look at the number of pills consumed or the number of people
3 using MDMA, even under an illegal situation, very few, very,
4 very few wind up dying.

5 Q. Then there is a concern with depression discussed a few
6 different times in the report, and they refer to it a few
7 different ways, suicide Tuesday. Does MDMA cause depression?

8 A. I do not believe MDMA causes depression. In order to make
9 a diagnosis of clinical depression, you must remain clinically
10 depressed for at least two weeks straight. Most of these
11 research studies that showed midweek blues do not ever publish
12 saying there was persistent depression of two weeks' duration,
13 that's one.

14 Two, my NIDA-funded research, we also inquire very
15 carefully about people's mood after using Ecstasy and the
16 duration of the effect from it, do they get depressed from it,
17 and my next paper will focus on that data. In there, what we
18 found is that people before they ever used Ecstasy, people with
19 histories of depression or anxiety or family histories of
20 depression or anxiety in primary relatives, these are the
21 people almost all of whom will wind up saying they will have a
22 day or two of depressive mood after use. People who don't have
23 that history are much, much less likely to ever even describe
24 post-Ecstasy use as causing depression.

25 Q. So, in sum, could an objective scientist familiar with the

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0C64MCC5 Halpern - direct

1 studies today affirm the report's conclusion that MDMA is more
2 harmful than cocaine?

3 A. If they are not, if they are aware of all of the current
4 literature that's been published, I don't believe that would be
5 possible for them to reach such a determination.

6 Q. Could such an objective scientist again assuming
7 familiarity with all of the scientific studies today affirm
8 that MDMA causes brain damage?

9 A. No.

10 Q. In sum, would you say the state of the debate has shifted
11 since 2001?

12 A. Yes. We have a better understanding of the harms from
13 MDMA. There are harms from MDMA. Anything can be used or
14 abused. But the types of ominous conclusions as contained and
15 summarized in that report are no longer accurate.

16 MR. MICHELMAN: Thank you very much.

17 THE COURT: Cross-examination, Mr. Chung.

18 MR. CHUNG: Mr. Kobre will be conducting the
19 examination.

20 MR. KOBRE: With the court's permission, I would like
21 to position myself over here.

22 THE COURT: Wherever is going to work best.

23 MR. KOBRE: Thank you, your Honor.

24 CROSS EXAMINATION

25 BY MR. KOBRE:

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0C64MCC5 Halpern - cross

1 Q. You have heard of Andrew Parrott, right?

2 A. Yes.

3 Q. You are aware that Professor Parrott is currently a
4 professor in the department of psychology at Swansea
5 university?

6 A. Yes.

7 Q. You are aware that Professor Parrott is on the editorial
8 boards of several journals?

9 A. Yes.

10 Q. That those journals include a journal by the name of
11 Current Drug Abuse Reviews?

12 A. I was not aware of that.

13 Q. A journal, Drug and Alcohol Dependence?

14 A. Yes.

15 Q. And he is on the editorial board as well of a journal
16 called Human Psychopharmacology?

17 A. I am now.

18 Q. An another journal called Journal of Psychopharmacology?

19 A. Yes.

20 Q. You are also aware that Professor Parrott has published
21 more than 50 peer review papers specifically regarding the
22 effects of MDMA, is that right?

23 A. I am not sure because this morning I remember hearing that
24 he was the authorize of 43 such articles.

25 Q. I don't recall that was what was said.

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0C64MCC5 Halpern - cross

- 1 A. I know he is very well published in his field, yes.
2 Q. You are aware of Dr. Glen Hanson?
3 A. Yes, of course.
4 Q. You are aware that Dr. Hanson is currently a tenured
5 professor in the department of pharmacology and toxicology at
6 the University of Utah?
7 A. I well remember when he was recruited to the University of
8 Utah after his tenure at NIDA, yes.
9 Q. He was an acting director of NIDA from 2001 to 2003, right?
10 A. Yes.
11 Q. Dr. Hanson has published more than 20 peer review papers
12 specifically regarding the effects of MDMA, right?
13 A. That sounds about approximately right.
14 Q. You also heard of Stephen Kish we have been talking about?
15 A. Yes, the University of Toronto professor.
16 Q. Professor Kish published in a number of peer review
17 journals?
18 A. Of course.
19 Q. Including a journal called Brain, right?
20 A. Yes.
21 Q. According to the resume you provided you have published a
22 total of two peer review journal articles specifically about
23 MDMA, is that right?
24 A. That's correct.
25 Q. You are in the process of conducting a study regarding the
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0C64MCC5 Halpern - cross

- 1 use of MDMA to treat anxiety in patients with cancer, right?
2 A. That's correct.
3 Q. That study involves administering actual doses of MDMA to
4 subjects in a laboratory environment, right?
5 A. In a laboratory setting, yes.
6 Q. You are conducting that study in your capacity as a
7 researcher at McLean University?
8 A. At Harvard Medical School, Harvard University at McLean
9 Hospital, yes.
10 Q. You have in the past received funding for that study from
11 an organization called MAPS, right?
12 A. The study of administering MDMA?
13 Q. Yes.
14 A. We received a small amount of money to help with the
15 initial protocol design but the actual funding for the study
16 has no MAPS involvement whatsoever. It's funded by one donor,
17 I mentioned private donors, this who I was thinking of, a
18 billionaire benefactor, Mr. Peter Lewis.
19 Q. You have received, there has been funding for that study
20 from an organization called MAPS, right?
21 A. That's correct.
22 Q. MAPS stands for Multidisciplinary Association for
23 Psychedelic Studies, right?
24 A. Yes.
25 Q. In fact, you received thousand dollars of dollars from MAPS

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0C64MCC5 Halpern - cross

1 in connection with the anxiety study, correct?

2 A. There were I think approximately thousands but probably not
3 more than \$20,000 over the time of that initial time.

4 Q. You received money from MAPS in connection with other
5 studies that you performed as well, right?

6 A. The only other funds that I received from MAPS was to help
7 complete data from my NIDA-funded career development ward that
8 took me to the Navaho Nation looking at the long-term cognitive
9 consequences of the religious use of peyote by native American
10 citizens. The bulk of that funding was still provided by NIDA.
11 Some funding was provided by MAPS.

12 Q. MAPS' public goal is to develop psychedelics and marijuana
13 into prescription medicines, right?

14 A. That's correct.

15 Q. In fact, developing MDMA into an FDA-approved prescription
16 medicine is MAPS' top priority?

17 A. I am not a representative of MAPS, but it's my general
18 impression that's true.

19 Q. MAPS was founded by an individual named Rick Doblin?

20 A. Yes, Dr. Doblin founded MAPS.

21 Q. Doblin is currently the executive director of MAPS?

22 A. Dr. Doblin is the director of MAPS.

23 Q. In fact, you have attended various MAPS events with Doblin,
24 is that right?

25 A. I have attended some of his events, yes. I have spoken at

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0C64MCC5 Halpern - cross

1 some of those events, yes.

2 Q. You attended the burning man festival with Doblin in 2005?

3 A. It may have been last year but I did go to help as an
4 arranger for the burning man organization, to help with people
5 who have gotten in trouble with their drug use.

6 Q. That is with Doblin, he was there as well at that time?

7 A. No, he came at the very end of the event for a few days.

8 Q. Doblin's publicly professed goal is to help develop legal
9 context for the beneficial uses of psychedelics and marijuana,
10 right?

11 A. That is I think what you just asked me, yes, the idea is to
12 lawfully and legally explore the development of a substance for
13 its therapeutic prescription purposes, yes.

14 Q. In fact Doblin publicly advocates the legalization of
15 psychedelics and marijuana for personal growth for otherwise
16 healthy people, is that right?

17 A. I think that may be his personal opinion.

18 Q. In order to administer MDMA as part of your anxiety
19 studies, you had to obtain approval from the Drug Enforcement
20 Administration?

21 A. That was one of many agencies, I shouldn't say many
22 agencies, there is an institutional review board, there is the
23 administrators and senior faculty at the university and the
24 hospital, of course, very importantly, the Division of Public
25 Health of the Commonwealth of Massachusetts.

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0C64MCC5 Halpern - cross

1 Q. The reason why you had to secure Drug Enforcement
2 Administration approval was because MDMA is a Schedule I drug,
3 right?

4 A. Correct. The only lawful way to administer a Schedule I
5 substance in a research setting is to apply for a researcher's
6 registration both from the state in which you hope to perform
7 such research and federally from the Drug Enforcement
8 Administration.

9 Q. In addition to getting personal approval from the Drug
10 Enforcement Administration, you also, you or the sponsor of the
11 study also had to file a form with the Food and Drug
12 Administration, right?

13 A. That's correct, and I filed it as an investigator/sponsor
14 and received FDA number 76770 for the study.

15 Q. The form you filed with the FDA stated that MAPS and its
16 founder Rick Doblin would be the monetary sponsors of the
17 study, is that right?

18 A. That's not correct. Initially, they hold their own, this
19 is an IND number from the FDA, they hold number 63384 I believe
20 and they can then as a sponsoring agency use that IND number
21 for sponsored research. When we decided to not have MAPS'
22 involvement at all, then I was instructed to file my own
23 independent of MAPS' application to FDA, and that's what
24 occurred for 76770.

25 Q. What I am referring to is when the form was initially filed

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0C64MCC5 Halpern - cross

- 1 with the FDA, it stated that MAPS and its founder Rick Doblin
2 would be the monetary sponsors of that study, is that correct?
3 A. That is correct.
4 Q. You mentioned before that MDMA is a Schedule I drug?
5 A. Correct.
6 Q. And Drug Enforcement Administration has classified MDMA as
7 a drug that has a high potential for abuse with no recognizable
8 medical use in treatment in the United States, right?
9 A. There is a very strange history, of course, behind the
10 registration of MDMA as a Schedule I drug. It was in fact when
11 there were findings of fact by a DEA administrative law judge,
12 it was recommended to be placed into Schedule III and was
13 overruled.
14 Q. I am asking you is it the case that Drug Enforcement
15 Administration has classified MDMA as a drug that has a high
16 potential for abuse with no recognized medical use in treatment
17 in the United States?
18 A. Yes, they have classified that. I am sorry, I
19 misunderstood your question.
20 Q. In 2005, you applied for a Schedule I researcher's
21 registration from the DEA, right?
22 A. Correct.
23 Q. You filed that application specifically so that you could
24 perform research using MDMA, right?
25 A. Correct.

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0C64MCC5 Halpern - cross

1 Q. One of the reasons you applied was so you personally could
2 administer MDMA to subjects in the study, right?

3 A. It was so, yes, I could just do the research that I was
4 trained to do.

5 Q. Specifically so that you personally could administer that
6 drug to subjects, right?

7 A. Yes.

8 Q. Because without the Schedule I registration you could not
9 legally administer the drug to others, right?

10 A. Of course, that's true.

11 Q. Without the registration you couldn't even possess the drug
12 legally?

13 A. I myself personally may not have any physical possession of
14 the substance, that's correct.

15 Q. You did not disclose on your application for that Schedule
16 I registration that you had been involved prior that he had
17 been previously involved in a Drug Enforcement Administration
18 investigation, right?

19 A. I am unaware of an application form that asks me to do
20 that. We just fill out a very basic form then there is more
21 specific questions that would occur in a field interview.

22 Q. As part of the application process as well you were
23 interviewed by Drug Enforcement Administration representatives
24 at your office, right?

25 A. At my office and on hospital grounds, so in private and in

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(212) 805-0300

0C64MCC5 Halpern - cross

- 1 public places, yes.
2 Q. That was at McLean Hospital?
3 A. Yes.
4 Q. This meeting took place on March 10, 2005?
5 A. That sounds like the correct date.
6 Q. At the meeting, a DEA representative asked whether you had
7 ever been involved in a DEA investigation, right?
8 A. Correct.
9 Q. You stated no, right?
10 A. That's correct.
11 Q. The agent asked yet again, so no one has been asked yet
12 again whether you have ever been involved in a prior
13 investigation?
14 A. To my best recollection this question was asked once, and
15 as I described earlier, it was asked in this very busy public
16 setting of a busy pharmacy, not in my office privately.
17 Q. You recall being asked once whether you ever had been
18 involved in a DEA investigation, right?
19 A. In essence, yes.
20 Q. Your answer at that time was no, right?
21 A. That's correct.
22 Q. But in fact, you had been involved in a DEA investigation,
23 right?
24 A. That's correct.
25 Q. In fact, you were not only involved in the DEA

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0C64MCC5 Halpern - cross

1 investigation, you were the target of the investigation, right?

2 A. This is a legal term that I would refer to my lawyer about.

3 As far as I know, it was an investigation for the prosecution

4 of Mr. Picard and the people who were put on trial. But if you

5 tell me that I was, then I will accept it.

6 Q. The investigation involved an investigation into not only

7 Mr. Picard's criminal activity but into your criminal activity,

8 isn't that right?

9 MR. RORTY: Your Honor, objection. I would refer the

10 court to the government's proffer with respect to this subject.

11 The proffer indicates Dr. Halpern represented to DEA personnel

12 that he had never been involved in a DEA investigation. The

13 nature of the involvement goes beyond the court's order and

14 indeed the government's own proffer.

15 MR. KOBRE: The extent of the misrepresentation

16 obviously, one of the major factors is the extent of Dr.

17 Halpern's involvement in that investigation. So, the

18 government would request just --

19 THE COURT: I am going to permit the witness to answer

20 this question, but we are not going to have a mini trial on Dr.

21 Halpern's involvement in another proceeding.

22 Do you have the question in mind.

23 THE WITNESS: I guess repeat it please.

24 BY MR. KOBRE:

25 Q. You knew at the time that the DEA investigation that you

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0C64MCC5 Halpern - cross

1 had been involved in was an investigation not only into the
2 criminal activity of others, but into your own criminal
3 activity.

4 A. Not only was I aware of that, my lawyer told me that these
5 investigators that were coming to the hospital would know about
6 it. I was instructed to not disclose anything publicly about
7 what had just transpired in a grand jury.

8 (Continued on next page)

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0C6UMCC6 Halpern - cross

1 Q. As part of that investigation, you met with DEA agents on
2 at least seven occasions, right?

3 A. That's correct.

4 Q. You not only met with DEA agents, but on several occasions,
5 you met with Assistant United States Attorneys from the
6 Northern District of California, isn't that right?

7 A. Yes.

8 Q. One of those several occasions, when you met with DEA was
9 on November 30, 2000, right?

10 A. I can't recall my memory of the exact date.

11 Q. On that occasion, you claimed to have no knowledge that
12 Picard was involved in LSD trafficking, right?

13 A. If that was the first such meeting, I may have stated that.
14 I think I did, and that was not true, and I absolutely made
15 clear that that was a mistake, that was not true to those
16 investigators later.

17 Q. In fact, on that occasion you told the DEA agents that you
18 had no knowledge that Picard was involved in any criminal
19 activity at all?

20 THE COURT: Sustained.

21 Move on to something else.

22 MR. KOBRE: Just one moment.

23 THE COURT: Take your time, Mr. Kobre.

24 Is this an appropriate time to take a short recess?

25 MR. KOBRE: I am OK continuing, your Honor.

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0C6UMCC6 Halpern - cross

1 THE COURT: Fine.

2 BY MR. KOBRE:

3 Q. Dr. Halpern, you stated on your resume that you received a
4 research grant award from an organization known as the Heffter
5 Research Institute, right?

6 A. That's right.

7 Q. And Heffter institute provided support for your research
8 into the cognitive effects of substance abuse in native
9 Americans, right?

10 A. No, that's not right. They provided funding for my
11 research on the cognitive performance of native Americans who
12 have lawful access to the non-drug sacramental use of peyote.

13 Q. And the subjects of this study were members of the native
14 American church, right?

15 A. That's correct.

16 Q. The study was to determine the cognitive effects of peyote
17 on those individuals, right?

18 A. That's correct.

19 Q. And the study ultimately led to the publication of an
20 article, right?

21 A. That's correct.

22 Q. And that article was published in 2005, right?

23 A. That's correct, in a peer review journal.

24 Q. The Heffter Research Institute is located in Santa Fe, New
25 Mexico, right?

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0C6UMCC6 Halpern - cross

1 A. Yes.

2 Q. And one of the goals of the Heffter Institute is developing
3 knowledge regarding the safe use of classical hallucinogens, is
4 that right?

5 A. I believe so, yes.

6 Q. In another one of those meetings with the DEA agents, one
7 of those meetings took place on March 26, 2001. Do you recall
8 that?

9 A. There were so many meetings, but I will take your word that
10 it was on that day.

11 Q. At that meeting, you told agents of the DEA that you
12 received two grants from the Heffter Institute, right?

13 A. I think so.

14 Q. And you told them that the first grant was issued in 1998,
15 right?

16 A. That sounds right.

17 Q. And that grant was for \$30,000, right?

18 A. That's correct.

19 Q. And it was a grant related to your peyote study?

20 A. That's right.

21 Q. And peyote is another Schedule I controlled substance?

22 A. False. False. Just absolutely false. It is a Schedule I
23 drug of abuse and a Schedule I controlled substance for
24 everybody else, but for native American who have limited
25 sovereignty it is not a Schedule I drug.

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0C6UMCC6 Halpern - cross

- 1 Q. I did not ask you for native Americans, I asked you if
2 peyote was a Schedule I controlled substance. Is that true?
3 A. For everybody but the people that are using peyote that I
4 was studying, in that context, it was a Schedule I drug.
5 Q. And peyote is a hallucinogen, right?
6 A. For outside of the scope of my research in that matter,
7 yes.
8 Q. I am only asking you, is peyote a hallucinogen?
9 A. Yes.
10 Q. And LSD is hallucinogen, right?
11 A. Yes.
12 Q. And MDMA is a hallucinogen, right?
13 A. MDMA is currently scheduled in the Controlled Substances
14 Act as a hallucinogen but, scientifically, it doesn't meet the
15 full definition of "hallucinogen."
16 Q. But it has hallucinogenic properties?
17 A. It has some, yes.
18 Q. You in fact did receive a \$30,000 grant from the Heffter
19 Institute?
20 A. I did.
21 Q. And that was in 1998?
22 A. That's right.
23 Q. On March 26, 2001 when you met with agents of the DEA, you
24 initially told them that you had no knowledge of the origins of
25 that money, is that right?

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0C6UMCC6 Halpern - cross

1 MR. RORTY: Objection, your Honor. I believe that
2 this goes beyond the terms of the Court's order and the
3 government's proffer.

4 MR. KOBRE: Your Honor, it directly goes to another
5 misrepresentation of Dr. Halpern, directly.

6 MR. RORTY: I would note that in the government's
7 proffer is the description of alleged criminal conduct. That
8 proffer includes acceptance of money from a research agency and
9 describes the circumstances of the acceptance of those funds.
10 In the government's proffer concerning false statements to
11 agents and prosecutors, the description of the false statements
12 is simply the nature and extent of his involvement with
13 individuals who were involved in the manufacture and
14 trafficking of LSD.

15 MR. KOBRE: And that is exactly where this line of
16 questioning is proceeding.

17 THE COURT: It is taking on the hallmarks of a mini
18 trial.

19 Move on.

20 I am going to sustain the objection.

21 BY MR. KOBRE:

22 Q. Dr. Halpern, you yourself have used drugs on multiple
23 occasions, isn't that right?

24 MR. RORTY: Objection. Relevance.

25 MR. KOBRE: Your Honor, it goes to bias of the

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(212) 805-0300

0C6UMCC6 Halpern - cross

1 witness.

2 THE COURT: Sustained.

3 Q. Well, Dr. Halpern, you testified before that on March 10,
4 2005, you met with interviewers from the Drug Enforcement
5 Administration, right?

6 A. Yes.

7 Q. And that was in connection with your application to become
8 a Schedule I researcher, right?

9 A. No, to become a Schedule I registrant.

10 Q. Correct. Is that right?

11 A. Yes.

12 Q. After that meeting, four days later on March 14, 2005, you
13 called a DEA investigator regarding your application to become
14 a Schedule I researcher, right?

15 A. That's correct.

16 Q. And that was just four days after the agents had
17 interviewed you at your office, right?

18 A. Correct.

19 Q. You had learned by that point that the DEA investigators
20 believed that you had lied to them at the interview, right?

21 MR. RORTY: Your Honor, I am going to object again,
22 beyond the scope of the government's proffer and covering
23 ground that I believe has been well covered in this
24 examination.

25 THE COURT: Where are you going, Mr. Kobre?

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0C6UMCC6 Halpern - cross

1 MR. KOBRE: Your Honor, it goes to bias of the
2 witness. It is not a very lengthy line of questioning.

3 THE COURT: How is it relevant whether he learned at
4 that point four days later that government agents believed he
5 lied to them at the interview?

6 MR. CHUNG: Your Honor, if I may?

7 THE COURT: Go ahead, Mr. Chung.

8 MR. CHUNG: On direct examination, Dr. Halpern
9 testified that there was a reason for lying, that he answered
10 no to the DEA investigators' question of were you involved in a
11 DEA investigation? His reason, his testimony was that his
12 lawyer had instructed him or advised him that the investigators
13 would know and that he could, in effect, misrepresent to the
14 investigators that he had not been involved in that DEA
15 investigation.

16 This line of questioning, and it will be a limited
17 line of questioning, is intended to rebut that testimony.

18 MR. RORTY: I just heard the government proffer that
19 this line of questioning was to bias.

20 THE COURT: I am going to permit this limited inquiry.

21 Go ahead, Mr. Kobre.

22 BY MR. KOBRE:

23 Q. Dr. Halpern, you had learned by that point that the DEA
24 investigators believed that you had lied to them at the
25 interview, right?

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0C6UMCC6 Halpern - cross

1 A. Yes.

2 Q. And during the phone conversation, you tried to convince
3 them that they had misunderstood you, right?

4 A. Or that I had misunderstood them.

5 Q. But just several days earlier, as you testified before,
6 they asked you a clear question, have you ever been involved in
7 a DEA investigation, right?

8 A. That is not the phrase that they used. You are creating a
9 question that they did not ask.

10 Q. Well, you just testified earlier that they asked you
11 whether you had ever been involved in a DEA investigation?

12 A. They inquired whether there was an investigation. I don't
13 recall it being asked the way you are phrasing it. So I guess
14 that I should --

15 Q. Now, in this phone conversation, you tried to convince them
16 that it was all a misunderstanding, right?

17 A. Indeed.

18 Q. And you told them that you don't want anyone in the DEA to
19 think that you are not doing what you should be doing, right?

20 A. There was no reason for me to lie to them or deceive them
21 with the intent of providing them misdirection.

22 Q. You then asked the interviewer during this phone
23 conversation how high they wanted you to jump? Do you recall
24 saying that?

25 A. Absolutely. And what I meant by that was that I had every

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(212) 805-0300

0C6UMCC6 Halpern - cross

1 interest in doing this research by the book.

2 Q. Now, you then withdrew your application to become a
3 Schedule I researcher with the DEA, right?

4 A. I eventually withdrew my application for registration, for
5 Schedule I.

6 Q. And another researcher applied, right, for DEA
7 registration?

8 A. Correct.

9 Q. But that was for precisely the same study as you had
10 originally applied, right?

11 A. Yes.

12 Q. The research protocols stayed the same?

13 A. That's right -- no. It was modified to make it extremely,
14 extremely clear that this other investigator would be in charge
15 of all of the responsibilities involving the handling of MDMA
16 and that I would not be.

17 Q. Right. So the only thing that changed about the study was
18 the name of the researcher?

19 A. No. The only thing that changed was that that task was
20 then added to one of my research colleagues.

21 Q. Under the new application, you were not to have any access
22 to the MDMA, right?

23 A. That's what I wrote, yes.

24 Q. That's correct?

25 A. Yes, that's correct.

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(212) 805-0300

0C6UMCC6 Halpern - cross

1 Q. So the bottom line is, since you do not have a Schedule I
2 registration, you are not permitted to dispense MDMA as part of
3 the study, right?

4 A. I am not permitted to physically dispense it, but if I
5 enroll a subject in my study, then indirectly I guess I am.

6 Q. Physically --

7 A. Physically, I don't want to go anywhere near touching it.

8 Q. When conducting a drug study, particularly of a
9 hallucinogen, it is your position that the researcher must take
10 the drug himself or herself in order to conduct the research,
11 right?

12 A. That's not written into my protocol to do something like
13 that, no.

14 Q. No. I am asking you, is it your position that a
15 researcher, when conducting a study, a drug study, particularly
16 of a hallucinogen, the researcher must take the drug him or
17 herself in order to properly conduct such research?

18 A. No.

19 Q. Well, in 2008, do you recall that you gave an interview to
20 a paper called The Phoenix? Do you recall that?

21 A. I do.

22 Q. In that interview you discussed your research on the
23 effects of peyote on members of the native American church?

24 A. Yes.

25 Q. And in that interview you were asked if you yourself had

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(212) 805-0300

0C6UMCC6 Halpern - cross

1 ever tried peyote?

2 A. Yes.

3 Q. You said you did take peyote and you would not have been
4 able to do the research if you had not, do you recall that?

5 A. Of course.

6 Q. Your study regarding MDMA cancer patients was originally
7 funded by MAPS, right?

8 A. It was initially funded by MAPS.

9 Q. But MAPS no longer funds the study as you testified before,
10 right.

11 A. That's correct.

12 Q. MAPS no longer funded the study because McLean Hospital
13 refused to allow the study to go forward due to the involvement
14 of MAPS, right?

15 A. During the short tenure of one president of McLean, it was
16 his individual decision to no longer accept funds from MAPS --
17 one individual, not McLean.

18 Q. But you couldn't conduct the study at McLean so long as
19 MAPS was funding it, right?

20 A. That's correct.

21 Q. As a result, MAPS directed one of its major donors to fund
22 the study instead, right?

23 A. Yes.

24 Q. And that study is funded by, as you mentioned before, an
25 individual named Peter Lewis?

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0C6UMCC6 Halpern - cross

- 1 A. Correct.
2 Q. Since 1991, Lewis has contributed \$5 million to the ACLU
3 you fight drug laws, right?
4 A. I have no knowledge of that. I don't know.
5 Q. Well, Lewis has made large contributions to drug
6 legalization campaigns throughout the United States?
7 A. I don't follow this man's pattern of donations. I know he
8 is a philanthropist.
9 Q. You are aware that he has given a great deal of money to
10 MAPS, right?
11 A. Actually, I am not. The only major donation that I knew
12 that he was going to make was actually potentially to my study,
13 and then he wound up donating it directly to me.
14 Q. So it is your testimony today that you don't know that
15 Lewis donated money to MAPS?
16 A. I am sure that he has, I just don't know the amount.
17 Q. And you are aware that Lewis was chairman of the board of
18 the Marijuana Policy Project?
19 A. I knew that he had involvement in the Marijuana Policy
20 Project. And the only other thing that I know was that he was
21 the biggest donor to the Guggenheim Museum.
22 Q. Now you testified earlier that you have written a total --
23 not written -- you have published a total of two peer review
24 journal articles specifically concerning MDMA, right?
25 A. I have also published -- yes, yes.

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0C6UMCC6 Halpern - cross

- 1 Q. Specifically --
2 A. Peer review or journal articles?
3 Q. Peer review journal articles?
4 A. Yes, two.
5 Q. One of those studies was published in 2004, right?
6 A. I believe so.
7 Q. That was your initial study regarding MDMA, right?
8 A. I think it was 2006.
9 Q. And the other, there was another study that has not yet
10 been published about MDMA that we talked about earlier, the
11 2010 study?
12 A. Correct.
13 Q. And the 2010 study is entitled "Residual Neurocognitive
14 Features of Long-term ecstasy Users with Minimal Exposure to
15 Other Drugs," right?
16 A. Yes.
17 Q. And your 2004 paper was entitled "Residual
18 Neuropsychological Effects of Illicit MDMA in Individuals with
19 Minimal Exposure to Other Drugs," right?
20 A. Yes.
21 Q. In your 2010 study, one of the tests used was called
22 revised strategy applications test, right?
23 A. Yes.
24 Q. That is the RSAT?
25 A. Yes.

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0C6UMCC6 Halpern - cross

- 1 Q. You found in your 2010 study that Ecstasy users had a
2 significant deficit on that test, right?
3 A. They had a statistically significant difference.
4 Q. Well, you concluded in that study that the proportion of
5 "brief items on the RSAT was strikingly and significantly lower
6 in heavy Ecstasy users," is that right?
7 A. That's right.
8 Q. Your 2004 paper states that it provides evidence that
9 "heavier and/or more prolonged MDMA use may be associated with
10 residual cognitive deficits," correct?
11 A. That's right.
12 Q. In your 2004 study, the median lifetime episodes of MDMA
13 use among the MDMA user group was 60, right?
14 A. That sounds correct.
15 Q. In your 2010 study, the median lifetime episodes of MDMA
16 use in the MDMA user group was 43.5, right?
17 A. That's right.
18 Q. So the median lifetime episodes of MDMA use among MDMA
19 users was nearly one-third less in your 2010 study than it was
20 in your 2004 study, right?
21 A. That's correct. It sounds right.
22 Q. Now, in your 2010 study, the median number of days since
23 last Ecstasy used when tested for the Ecstasy user group was
24 121, right?
25 A. Correct.

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0C6UMCC6 Halpern - cross

1 Q. In your 2004 study, the median days since last Ecstasy use
2 when tested for the Ecstasy user group was 65 for heavy users,
3 right?

4 A. That sounds correct.

5 Q. So the median days since last Ecstasy use when tested for
6 the Ecstasy user group in the 2010 study was approximately half
7 that in the 2004 study, is that right?

8 A. Yes.

9 MR. KOBRE: Nothing further.

10 THE COURT: Redirect examination?

11 MR. RORTY: I have no questions on redirect.

12 Thank you.

13 THE COURT: I have a couple of questions.

14 What are the neurological physical effects of cocaine
15 as opposed to MDMA?

16 THE WITNESS: Well, I think the most glaring example
17 of contrasts would be in evidence of stroke, of lesions in the
18 brain that can be visualized on an imaging. Cocaine is
19 basically constrictive; it will cut off the supply of blood.
20 And through heavy and excessive use, this can actually cause
21 tiny strokes that wouldn't even be known by the patient over
22 time, but through many, many years of use, you will see that on
23 imaging, you will see that a lot of these heavy users -- and
24 this sort of thing is not found in MDMA users.

25 I also did neurological examinations of subjects in my

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1 NIDA funded study because of concerns of these early claims of
2 Parkinson's like disease or abnormal movements in Ecstasy
3 users, and so I thought it would be important to do a
4 neurological exam on all of these people to see if I could
5 illicit that, and I didn't on any of the subjects in the study.

6 THE COURT: How do the harms of marijuana compare to
7 MDMA?

8 THE WITNESS: I think the harms from marijuana come
9 quite often because people who get into problem use, it can
10 persist and become daily users, repetitive users, heavy users.
11 Many patients that would become marijuana dependent and smoke
12 daily for decades, but I have never met any patient who abused
13 MDMA, Ecstasy come to me and say, oh, yeah, I have been a daily
14 user of MDMA for the last year. So that is the difference in
15 types of problems from it.

16 I think what makes it so hard to compare one drug with
17 another is the pattern of use, pattern of abuse, the dosage
18 range that they use. In some ways, we could say that MDMA is
19 more dangerous than marijuana, for example, the dose predicted
20 to be lethal in marijuana is much, much higher than it is with
21 MDMA. It is only theoretical in marijuana. It is estimated to
22 be eight kilograms consumed at once. So I don't think that
23 there are any cases in the literature of marijuana overdose
24 cause of death but, of course, we do have that from Ecstasy.

25 So depending on what part of the toxicity we are

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1 looking at, what part of harm we are looking at, one may be
2 perceived as more potentially dangerous than the other, but I
3 believe Dr. Curran drilled down to what would be the most
4 accurate assessment, that for the majority of users consuming
5 MDMA on one or two times a month, it is probably much less
6 dangerous than the chronic consumption of marijuana.

7 THE COURT: It terms of the trend of MDMA use, can you
8 characterize what your studies have revealed between 2001 and
9 today?

10 THE WITNESS: Thank you for asking that question,
11 because when I originally proposed my study to the government,
12 there was a large scene of Ecstasy exclusive users in the
13 Greater Salt Lake City area and by the time of my funding, my
14 case finder who I worked very closely with, couldn't find the
15 same abundant number of people. It made it much harder.

16 So I had promised NIDA that we would get over 200
17 subjects, but my final data set, that is the one that is in the
18 Impress paper, and you will notice that the number is smaller
19 because this population dried up. It was much harder to find
20 them. So by that measure, the trend, I directly experienced in
21 the collection of this data was that the use actually went
22 down.

23 THE COURT: To what do you attribute that?

24 THE WITNESS: In part, it has to do with the social
25 mores of the area. We heard earlier testimony that 99.9

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1 percent of Ecstasy users are polydrug abusers. And here you
2 have a study of a number of people that are pure Ecstasy users.

3 Salt Lake City is the headquarters of the Church of
4 Latter Day Saints, and it is very clear that the use of alcohol
5 is forbidden, and drugs like marijuana have been clearly
6 forbidden. And this filtered into the mores of the culture of
7 the area.

8 I actually interviewed people born and raised
9 atheists, but their parents and themselves have never even
10 tried alcohol once in their lives, and this happened a number
11 of times -- something that I think I very rarely encountered
12 elsewhere in the country. But it was quite a public campaign
13 against MDMA, and it became quite clear that MDMA is forbidden.
14 It was not on the forbidden list for the Church of Latter Day
15 Saints for a long time and then it was. So the experience and
16 the instructions to stay away from this drug was better
17 absorbed by the community. I think that was one part of the
18 reason why it changed.

19 THE COURT: Are you familiar at the current time with
20 what the national trends are in terms of the use of MDMA?

21 THE WITNESS: I am.

22 THE COURT: What are they?

23 THE WITNESS: There is very good year-to-year surveys
24 that come out of the University of Michigan, Monitoring the
25 Future Study which is funded by NIDA. And what we see is a

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1 trend of modest use amongst teenagers. Look at the Sanchez
2 study, the national survey of drug use, the use of
3 hallucinogens has been low or stable. In some years it trended
4 up a little bit, but it has never grown exponentially year to
5 year.

6 THE COURT: Earlier on, I think on cross-examination,
7 you described MDMA as being on Schedule I as a hallucinogen.
8 And you said it had some hallucinogenic properties. What is
9 the distinction, if any, that you are drawing there?

10 THE WITNESS: The important one is that when people
11 take what we term a classical hallucinogen like mescaline or
12 LSD, there is a loss of control, a loss of ego-control, this
13 dissolving of sense of self. This does not occur under the use
14 of MDMA. So people under the influence of MDMA are still aware
15 of who they are, and the type of impulsivity that they do is
16 not based on that they have lost their sense of self. This
17 does occur from classic hallucinogens. It does not occur with
18 this drug, MDMA.

19 THE COURT: Is there a debate today among researchers
20 as to whether or not MDMA is in fact a hallucinogen?

21 THE WITNESS: I think there is a consensus that the
22 use of either empathogen -- or entactogen is the more accurate
23 term -- and when we look at peer review publications, I think
24 we will see a trend year to year of more use of that term. It
25 is very difficult in this field to use the term "hallucinogen"

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1 in and of itself because even the drugs that are labeled
2 classical hallucinogens do not induce hallucinations typically,
3 so this definition is one that is wrought with a lot of
4 complications. But, scientifically, we are still labeling it
5 this way, even though we understand it is not very accurate.

6 THE COURT: In looking at the paper that you are about
7 to publish, you find little evidence of decreased cognitive
8 performance in MDMA users, correct?

9 THE WITNESS: Correct.

10 THE COURT: But you also state in that paper -- and I
11 am quoting now, I think, "This finding contrasts with many
12 previous findings including our own." That suggests to me that
13 there is an ongoing debate and no clear consensus, but would
14 you comment on what you meant there?

15 THE WITNESS: When we were referring to other
16 research, we really were referring to much of what you heard in
17 my testimony today which is that the type of excessive deficits
18 that were reported in small studies not found. And when we
19 were referring to ourselves, we are referring to the one
20 earlier publication in which we found deficits suggestive of
21 impulsivity on the Revised Strategic Application Test where we
22 did not replicate those findings.

23 Those results, by the way, on that one specific
24 measure are all within the range of normalcy. The test was
25 actually designed for people with traumatic brain injury, so we

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1 don't even have a good sense of when this type of test is
2 applied in drug abuse. It is a relatively test. It is a task
3 demanding task. I can quickly tell you what it is. It is hard
4 to do.

5 You are given only 10 minutes and you have one pile of
6 papers where you have to add up the number of items, another
7 pile where you have to draw a copy of a complicated diagram
8 and, a third pile where you write down like a phrase that's
9 above it. And if on any given page, if you see a frowny face,
10 you are not supposed to write anything on that page. And we
11 tell you that whether the task is easy, moderately difficult or
12 very difficult, they are all going to be scored the same, go.
13 You will see papers flying all over the place.

14 The point is to see if can you figure out the strategy
15 that is going to get you to do it the best. Part of the
16 trick -- we don't even tell people -- the first two pages that
17 you do, we are not even going to score it. You see some people
18 carefully filling out the first few pages, and they are not
19 getting what needs to be done to get the highest possible
20 score.

21 So in an earlier study with a much smaller number of
22 individuals, some of the heavy users did worse. And we thought
23 it was an example of impulsive decision-making and not the best
24 strategy. And we are still left thinking it may be that these
25 very heavy users, that there was something impulsive about them

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1 to begin with probably before they ever took the Ecstasy. And
2 that's whether the limitation would work, so we want to repeat
3 this test more in this population.

4 THE COURT: This morning we talked at length about
5 David Nutt's studies, and what is your assessment of those
6 studies by David Nutt?

7 THE WITNESS: I believe I also cited the 2010 paper to
8 the Court also. I think Dr. Nutt's report is quite relevant
9 because it is not just a collection of talking heads voting
10 their opinion. These are all very serious scientists that had
11 to think very carefully about how we were going to fill out
12 these measures when they came for the actual gathering.

13 Rather than go with the prevailing desired opinion
14 probably for a man in his position, he bravely forged ahead and
15 let the chips fall where they may -- what a good scientist
16 should do -- and he paid the price of losing his position even
17 for just stating the facts as he clearly saw them with his
18 colleagues. I think it is a very important paper for the Court
19 to consider.

20 THE COURT: How does the age profile of MDMA users
21 compare to other drugs such as cocaine, marijuana or
22 methamphetamines?

23 THE WITNESS: I think most people who have taken
24 Ecstasy have tried marijuana, in general, before MDMA. And so
25 an older group of people are using MDMA -- late teens, college

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1 years, early adulthood, and then the use tapers off. So it is
2 much more unusual for me to interview people in their 30s or
3 40s who have used MDMA. But marijuana use may persist, and
4 those that start using cocaine and methamphetamine, well, it
5 won't matter at what age they start, if they are using it, they
6 will quite often relapse to it later in life too.

7 THE COURT: The sentencing commission in its report
8 reflected the fact that MDMA was targeted at the youth. Do you
9 agree with that?

10 THE WITNESS: I don't agree with that. It appears to
11 be a misunderstanding of the subculture of these all night
12 dance parties. In 2001, there was a tremendous amount of
13 public outcry and Anti-rave Act came out. The term "rave" was
14 something new. Obviously, dance parties will attract younger
15 people. And yet unlike other drug using populations, this
16 group of users welcomes non-users. So for me to do this study
17 that we have heard about today, to find a large group of people
18 who don't use any drugs at all is remarkable in comparison to
19 my experience of using other drug using people.

20 For example, I handed out flyers at one of these all
21 night dance parties to try to get people to come to my study
22 and I saw this young man dancing with glow sticks and looking
23 wrapped up into himself. And he shows up at my study, and I
24 thought, for sure, this is an Ecstasy guy. And it turns out
25 that he just came back from mission. He has never used any

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1 drugs in his life, but he just loves dancing and he loves being
2 accepted from people that are different from him. I will never
3 forget that, because I am not used to seeing that when I have
4 worked in detox centers and longer-term residential programs
5 for drug abusers. It is different. It is what is attracting
6 people is not the Ecstasy use, it is the entire environment
7 that they are enjoying.

8 THE COURT: Thank you, Dr. Halpern.

9 Do counsel have any questions that they would like to
10 pose in light of the Court's inquiry of the witness.

11 Defendant first.

12 Mr. Michaelman.

13 MR. MICHAELMAN: Yes, your Honor.

14 THE COURT: Why don't you stand up and take the
15 podium.

16 REDIRECT EXAMINATION

17 BY MR. MICHAELMAN:

18 Q. Dr. Halpern, the judge asked you about your discussion of
19 the discrepancy between a couple of different studies that you
20 yourself noted in the 2010 paper. Could you characterize the
21 extent or the range of the debate among different studies? How
22 big of a disagreement are we talking about here in terms of
23 studies of cognitive impairment?

24 A. The disagreement is over the types of mild decreases in
25 cognitive performance whether or not -- they may be

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Halpern - redirect

1 statistically significant, but are they functionally
2 significant, just in that sphere? I think, in general, there
3 is consensus that there is evidence of severe brain damage now.
4 There is no debate about that anymore. We are just not seeing
5 that. The debate is in the area of these mild performance
6 decrements that do not appear to be functionally significant.
7 Q. We have heard today and in questions asked by the
8 government that there was some acknowledgment in the 2001
9 report that there was some debate even then. Would you compare
10 the range you have just described about the debate about
11 cognitive impairments from MDMA? Can you compare that to the
12 type of debate that might have been going on in 2001?

13 A. Yes. Very clearly, the debate as presented in the report,
14 I think they are to be commended for acknowledging that type of
15 debate, but that debate does not exist today. The evidence of
16 severe neurocognitive impairments, I think that you can see it
17 in the comprehensive meta-analysis report of Rogers of 2009.
18 It just doesn't hold water anymore. It is not like that
19 anymore, that extensive range of debate.

20 MR. MICHAELMAN: Thank you, Doctor.

21 THE COURT: Mr. Kobre.

22 MR. KOBRE: Just briefly.

23 THE COURT: Go ahead.

24 RECROSS EXAMINATION

25 BY MR. KOBRE:

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0C6UMCC6 Halpern - recross

1 Q. Dr. Halpern, in your 2010 paper, your criteria was designed
2 to exclude non-Ecstasy drug use as much as possible without
3 being so strict so as to excessively reduce the participant
4 pool, right?

5 A. That's correct.

6 Q. Now, most Ecstasy users use other drugs as well, right?

7 A. Yes, that's true.

8 MR. KOBRE: Nothing further.

9 THE COURT: Anything further, Mr. Michaelman?

10 MR. MICHAELMAN: No, your Honor.

11 THE COURT: Very well.

12 Dr. Halpern, you are excused as a witness. You may
13 step down.

14 (Witness excused)

15 THE COURT: Do you have another witness here at this
16 juncture we can get started?

17 MR. RORTY: Your Honor, the defense has no further
18 witness. I assume that question was addressed to the
19 government.

20 THE COURT: It was addressed to both parties. I was
21 certainly was under the impression that the defense has no
22 further witnesses.

23 Does the defense rest?

24 MR. RORTY: Yes.

25 THE COURT: Does the government have witnesses to

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0C6UMCC6 Halpern - recross

1 call?

2 MR. KOBRE: Yes, your Honor.

3 We call Professor Andrew Parrot.

4 THE COURT: We will work until 5 o'clock, and we will

5 resume.

6 Is that acceptable to the government?

7 MR. KOBRE: Yes, Judge.

8 THE COURT: And to the defense?

9 MR. RORTY: Yes.

10 ANDREW CHARLES PARROTT,
11 called as a witness by the government,
12 having been duly sworn, testified as follows:

13 DIRECT EXAMINATION

14 BY MR. KOBRE:

15 THE WITNESS: I am Andrew Charles Parrot.

16 I am a professor at the University of Swansea in the
17 United Kingdom.

18 THE COURT: You may inquire, Mr. Kobre.

19 Q. Good afternoon, Dr. Parrott.

20 A. Good afternoon.

21 Q. Dr. Parrot, can you just tell the Court just a bit about
22 yourself, where you are from and just a bit about your personal
23 background?

24 A. I am British, born in London, but now in Swansea in Wales,
25 working at the University of Swansea for the past six years.

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0C6UMCCF Parrott - direct

1 Before that I was at the University of East London.

2 Q. Let's start back a bit.

3 Where did you do your undergraduate studies?

4 A. That was at University of Durham in north of England.

5 Q. Did you receive any particular awards or honors at Durham?

6 A. I got a 2.i degree and I was one of the two highest
7 students.

8 Q. Then did you pursue your doctoral studies?

9 A. Yes. I got a research studentship at the University of
10 Leeds.

11 Q. What is a research studentship?

12 A. This was funded by the Medical Research Council and they
13 give out a limited number of these studentships for people to
14 study for a PhD.

15 Q. Among those at Durham, how many Medical Research Council
16 studentships were given out?

17 A. Well, two students from Durham were given these. One was
18 at London and one was at Leeds, and it was given by Leeds
19 rather than by Durham.

20 Q. Just, again, where did you receive your doctorate from?

21 A. My doctorate was from the University of Leeds, yes.

22 Q. What is your current position?

23 A. I am a professor at Swansea University.

24 Q. Can you please summarize for the Court your current major
25 areas of research?

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0C6UMCCF Parrott - direct

- 1 A. Well, for the past 18 years, I have been studying Ecstasy,
2 particularly in recreational users. Before that I studied
3 cigarette smoking and a range of other drugs.
4 Q. Before you were a full professor at Swansea, where were
5 you?
6 A. I was at East London, I joined there in the mid 1980s as a
7 senior lecturer and promoted to reader and then professor.
8 Q. What did you study at the University of East London?
9 A. That again was drug use. I have been studying various
10 types of drug use for many years now.
11 Q. Before that you were at the University of East London?
12 A. I was working for the Ministry of Defense in the U.K. in
13 their Institute of Naval Medicine where we were looking at the
14 effects of sea sickness drugs on naval personnel.
15 Q. And did that work involve work for the British government?
16 A. Yes. It was a British government funded study.
17 Q. You mentioned earlier you conducted research for
18 approximately 18 years regarding Ecstasy or MDMA.
19 Approximately how many papers have you published specifically
20 regarding MDMA?
21 A. I think that's a matter of debate, but I think it is
22 roundabout 50. I haven't counted it recently, I am afraid.
23 Q. Thank you.
24 A. I think it is 47 to be conservative, I guess.
25 Q. Were all of those published in peer review journals?

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0C6UMCCF Parrott - direct

1 A. Those, yes.

2 Q. Can you describe a little bit more specifically the main
3 areas of your research concerning MDMA?

4 A. I started various areas, particularly news and cognition,
5 the effects on feeling states and then cognition, I published
6 one of the first studies looking at memory in Ecstasy users,
7 and we published several studies in that area.

8 Q. Can you give the Court some examples of some of the
9 journals you published in?

10 A. Psychopharmacology, Drug and Alcohol Dependence, Human
11 Psychopharmacology, European Journal of Psychopharmacology--
12 all of the major psychopharmacology journals.

13 Q. Have you received any awards relate to your MDMA research?

14 A. Yes. I received two awards. One was in 1999 by the
15 British Association of Psychopharmacology. And I was given
16 their annual journal prize.

17 Q. Was that with respect to a specific research paper?

18 A. Yes. That was the paper where we published results of one
19 of the first studies to find memory deficits in young Ecstasy
20 users compared with young age match controls.

21 Q. You mentioned you had received two such awards?

22 A. Yes. The same award was awarded to Helen Fox and myself as
23 her supervisor in 2002.

24 Q. What was that? Was that also with regard to a specific
25 search paper?

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0C6UMCCF Parrott - direct

1 A. That was another Ecstasy research paper. Basically by that
2 time we had published a number of papers looking at the memory
3 deficits of Ecstasy users. We were also interested in why some
4 Ecstasy users reported problems and others didn't. So we split
5 the sample into two subgroups depending upon whether they
6 reported problems or not. So half of the group were people who
7 reported they had had problems with Ecstasy and the other group
8 reported they hadn't.

9 Q. When you said "problems," what kind of problems were you
10 referring to specifically?

11 A. Well, the question is very simple. It said, have you
12 developed any psychopharmacological problems as a result of
13 taking Ecstasy.

14 Q. And the results?

15 A. Some said yes, they had. Others said no, they hadn't. We
16 then gave everyone our usual battery of memory tests and what
17 we found was that there was no differences between the two
18 subgroups. Then when we split the group into dosage levels, we
19 found significant defects related to dosage. So for heavy
20 users who used over 100 times, reported the worst problems on
21 two particular tests. That was spatial memory and the logical
22 thinking test.

23 Q. Let's move on a bit, and then we will come back to this a
24 little bit later.

25 A. The basic thing was that both groups reported that. So

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0C6UMCCF Parrott - direct

1 even those who reported problems had that.

2 Q. Professor Parrot, are you on the editorial board of any
3 journals?

4 A. Yes. Drug and Alcohol Dependence, Human
5 Psychopharmacology, Journal of Psychopharmacology, and the
6 other one I have forgotten. I think it was mentioned earlier,
7 Current -- it used to be a web-based journal -- it is a fourth
8 journal anyway.

9 Q. Are you an academic reviewer for any peer review journals?

10 A. Yes. Over the years, I have reviewed for a large number of
11 journals. I think it is about 30 about now.

12 Q. Before we sort of get into the substance, can you give the
13 Court a brief background regarding the physical makeup of the
14 compound that is MDMA?

15 A. MDMA as is stimulant. It is methylenedioxymethamphetamine
16 derivative, so it is similar to the parent compound which is a
17 powerful stimulant drug, but interestingly, it has got what is
18 called a ring substituted, methylenedioxymethamphetamine
19 derivative, and that makes it somewhat different from
20 methamphetamine. In particular, it affects serotonin rather
21 than, preferentially, a dopamine.

22 Q. Before we discuss the current knowledge regarding the
23 effect of MDMA upon humans, I want to ask you, Professor
24 Parrott, how if at all the state of scientific knowledge
25 regarding the effects of MDMA has changed since 2001?

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1 A. Well, basically, the deficits reported in 2001 have been
2 confirmed in subsequent research. In addition to that, we
3 discovered a number of new areas of deficits which were not
4 known during 2001.

5 Q. Have the studies that have been performed since 2001
6 controlled for what you have heard before discussed here as
7 confounding factors?

8 A. Well, many of the studies before 2001 were interested in
9 particularly polydrugs confounds. When I reread my paper
10 published in 1998, I had written half a paragraph on the
11 potential compound of cannabis as a potential confound to MDMA.
12 And I discussed several papers which had been looking at that
13 as a confound. So people were aware of polydrugs confounds
14 before 2001.

15 Q. And there were papers that specifically controlled for
16 those confounding factors?

17 A. Well, they talked about it. They debated it. In
18 subsequent years, the studies are certainly becoming more
19 sophisticated in their attempts to investigate this as a
20 potential issue.

21 Q. Have any of the psychobiological deficits associated with
22 MDMA that were known in 2001 been called into question by
23 studies since that time?

24 A. No. All of the deficits reported in 2001 have been
25 subsequently confirmed by later studies.

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1 Q. Have there been recent studies with respect to the
2 neurotoxic effects of MDMA?

3 A. One particularly good study is the Kish study which is
4 probably one of the best today with the different factors and
5 it has a very large sample size.

6 Q. If you could tell us a little bit about the methodology and
7 the results that Kish found?

8 A. Well, they had two samples. One was 49. The other was 50.
9 So they had known users of Ecstasy and Ecstasy users. And they
10 put them through a standard sophisticated PET imaging
11 neuroimaging test, and they found deficits in all regions of
12 the cerebral cortex which as Val Curran described is the major
13 part of the brain in humans. And the other area which was
14 affected was the hippocampus.

15 Q. When you say "deficits," can you just explain a bit?

16 A. Well, they found reductions in the serotonin transporter
17 density which had been described earlier. And then the
18 cerebral cortex varied from minus 19 percent in some regions
19 to, I think it was around about minus 40 percent in other
20 regions. And they also found a deficit in the hippocampus, but
21 I can't remember what percentage that was.

22 Q. What does it mean to say that there was a reduction in
23 serotonin transporter?

24 A. As Val Curran described, this is the distal axon terminal.
25 Basically, the Raphe nuclei which is the base of the brain, you

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1 have serotonin neurons and they spend out very long thin axons
2 to the distal parts of the brain. So these are thought to be
3 very sensitive to damage. And then when you do these staining
4 of the cerebral cortex, you find there is a reduction in the
5 number of these serotonin transporters in the brains of the
6 Ecstasy users.

7 Q. So what is the reduction in the serotonin transporters mean
8 for the health of the axons?

9 A. Well, in functional terms, Kish also looked at memory
10 performance in their users, and they found that the memory
11 schools were impaired, so it was a functional aspect. I recall
12 they also found a correlation between these measures.

13 Q. You mentioned before that Kish was one of the better
14 studies. Can you just describe why you think Kish was a
15 particularly good study?

16 A. Well, it is a very long paper to read. Brain is a very
17 prestigious journal. It has to be an extremely good study to
18 be published in there. And they looked at so many potential
19 confounds in their subject selection and their analysis. For
20 instance, they looked at the effects of other drugs. In
21 particular, they looked at the potential confounds of
22 methamphetamine, the parent compound. And they concluded that
23 some of their users had used methamphet and others hadn't and
24 they split. They found that the imaging deficits, serotonin
25 deficits were present in both groups. So they concluded it

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1 wasn't methamphetamine use that led to the serotonin deficits.
2 It was the MDMA deficits.

3 Q. So what does the Kish study mean for the question of
4 neurotoxicity, whether MDMA causes neurotoxicity?

5 A. It is very clear evidence that Ecstasy users are suffering
6 from neurotoxicity in higher brain regions and the hippocampus
7 which is responsible for memory.

8 Q. You mentioned that since 2001, some studies have been
9 confirmed, some of the deficits have been confirmed, but you
10 also mentioned that there have been some new areas of
11 dysfunction that have been discovered. Can you tell us a
12 little bit about those?

13 A. One area that was not recognized in 2000 is prospective
14 memory, and the first reports were published in 2001.
15 Prospective memory is remembering to do something in the
16 future. So if you arranged to meet somebody at 5 o'clock for a
17 drink and you forget to turn up, that is a failure of
18 prospective memory. So prospective memory is very important
19 for organized intellectual activity. The first reports of
20 deficits published in 2001 and then subsequent group studies
21 have confirmed this in a number of trials.

22 Q. Are there any other new areas of dysfunction that have been
23 found since 2001?

24 A. Well, one area is in visual performance. There are two
25 Australian groups who recently linked together who found some

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1 subtle differences in visual illusions in Ecstasy users
2 compared to controls, and they relate this to deficits in the
3 occipital cortex which is the region in the back of the brain
4 responsible for visual processing.

5 Q. Is there any particular reason why a deficit in the
6 occipital cortex would be particularly relevant?

7 A. Well, it is important for vision. There is another study
8 published in 2005 where again they reported visual deficits.
9 So it is only two groups, so it is very new area, basically.

10 Q. You have heard described three or four sort of
11 chronological time periods that have been studied with respect
12 to MDMA, sort of an on drug period, then sort of followed
13 within the next week and then sort of a chronic effect. So I
14 would like to just walk through these three areas. If we could
15 just start with the on drug effects. Could you briefly
16 describe sort of on drug effects on humans?

17 A. It releases serotonin, so it is a very powerful stimulant.
18 You have arousal, increase in blood pressure, heart rate,
19 breathing rate. In mood terms, you can get very mood
20 intensification. The predominant moods tend to be positive.
21 You get feelings of euphoria. But you can also get negative
22 feelings, for instance, an increase in anxiety and tension
23 which, again, is not typical of many synapse stimulant drugs.

24 Q. What is serotonin syndrome?

25 A. Serotonin syndrome was first described in medications which

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1 lead to increased serotonin. And you had occasional reports of
2 persons suffering from serotonin syndrome which is due to too
3 much serotonin. And in particular, some of the effects include
4 overheating, confusion, also psychomotor aspects, repetitive
5 psychomotor actions. And if you give serotonin symptom lists,
6 there are reports of many users are probably experiencing a
7 mild form of the serotonin syndrome and, occasionally, you get
8 people more moderate and more severe aspects. And this is when
9 they need hospitalization to reverse the hyperthermia.

10 Q. Can MDMA use cause death?

11 A. It does cause death, unfortunately, yes.

12 Q. Can you describe how that would happen?

13 A. The two main forms of acute death, one is hyperthermia.
14 This is where people overheat and their bodies overheat and
15 that can cause an acute hyperthermic or overheating reaction.
16 There are some deaths which have been talked about.

17 The other cause of death is hyponatremia. And
18 basically when MDMA is taken, it can heat up the body and,
19 presumably, the brain as well, although that is a presumption.
20 And you get this increase in hyperthermic activity. People
21 feel hot. They also feel thirsty because they are feeling hot.
22 They are sweating. Many Ecstasy users feel this hyperthermic
23 response. So they drink water instead. And in addition, you
24 get confusion so people often are confused about how much water
25 they have drunk. So what can happen then, is they've got too

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1 much water in their body fluids.

2 In addition, MDMA stimulates for release of what is
3 called the antidiuretic hormone. I said that slowly. It is
4 antidiuresis. So it is against weeing or peeing. So this
5 means you wee less and you accumulate more fluids in your body.
6 So coupled with that, you can have this dangerous acute
7 reaction of hyponatremia.

8 Q. You referred before to some of the cognitive effects that
9 MDMA can have in an on drug user. Have you personally
10 performed any studies regarding those cognitive effects in an
11 acute user?

12 A. Sorry. I missed that.

13 Q. You mentioned before that MDMA could have some cognitive
14 effects in an on drug -- when a person is on MDMA. Have you
15 personally done any such study?

16 A. Yes. We have tested recreational Ecstasy users at dance
17 clubs and raves. In a 1998 paper we tested recreational
18 Ecstasy users using what was then an Apple message pad which
19 was then an early portable micro-computer I guess it was
20 superseded by more modern devices, but in 1998, it was state of
21 the art. It had a screen and we gave tests to people at the
22 club. One of the tests was a visual scanning test and the
23 other was a memory test. And what we found was, the Ecstasy
24 users were impaired on the visual scanning tests while at the
25 club and then compared with baseline and then they recovered

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1 two days later. So it had an acute effect in impairing visual
2 scanning. We gave interviews to people as well, and they
3 reported they found it difficult to focus on the task.

4 THE COURT: Is this a convenient spot to suspend for
5 the evening?

6 MR. KOBRE: Yes, it is, your Honor.

7 THE COURT: Dr. Parrot, I am going to ask you to step
8 down, sir. You are excused. And we will resume tomorrow
9 morning at 10 a.m.

10 Have a good evening, sir.

11 (Witness excused)

12 THE COURT: Are there any matters that counsel want to
13 raise before we conclude for the evening?

14 Any issues from the government?

15 MR. CHUNG: Not from the government.

16 MR. RORTY: Not from the defense.

17 THE COURT: We have the completion of Dr. Parrot and
18 one other witness?

19 MR. CHUNG: Yes. Dr. Hanson after Dr. Parrot.

20 THE COURT: There are no deadlines, but what is
21 counsel's best estimate of when we might conclude the taking of
22 evidence tomorrow?

23 MR. CHUNG: We estimate for Dr. Parrot another hour
24 and a half of direct examination and, obviously, I don't know
25 how long cross-examination is going to take. I can say that

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1 for Professor Hanson, it will be equal length, about hour and a
2 half to two hours of direct.

3 THE COURT: So we will definitely be working into the
4 afternoon, if not through it tomorrow and I have got the day
5 cleared. So we will work from 10 tomorrow morning.

6 MR. SPORN: Is this a good opportunity for me to
7 request that the hearing be transcribed pursuant to CJA?

8 THE COURT: Yes. You will complete a voucher. I will
9 sign it. You can get it straight away, because I am going to
10 invite the parties to make a further submission to me based
11 upon the transcript here. So you can request this on an
12 expedited basis.

13 I will see you tomorrow at 10 a.m.

14 Have a good evening.

15 (Proceedings adjourned until 10 a.m., December 7,
16 2010)

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	INDEX OF EXAMINATION	
1		
2	Examination of:	Page
3	HELEN VALERIE CURRAN	
4	Direct By Mr. Michelman	5
5	Cross By Mr. Chung	46
6	Redirect By Mr. Rorty	71
7	Redirect By Mr. Rorty	89
8	Recross By Mr. Chung	90
9	JOHN HAIM HALPERN	
10	Direct By Mr. Michaelman	106
11	Cross By Mr. Kobre	134
12	Redirect By Mr. Michaelman	169
13	Recross By Mr. Kobre	170
14	ANDREW CHARLES PARROTT	
15	Direct By Mr. Kobre	172
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		

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1 UNITED STATES DISTRICT COURT
1 SOUTHERN DISTRICT OF NEW YORK
2 -----x

3 UNITED STATES OF AMERICA

4 v. 09CR1136(WHP)

5 SEAN McCARTHY,
5 LARRY WARREN HOUGH,
6 Defendants.

7 -----x

8 New York, NY
8 December 7, 2010
9 10:10 a.m.

10 Before:

11 HON. WILLIAM H. PAULEY III

12 District Judge

13 APPEARANCES

14 PREET BHARARA
14 United States Attorney for the
15 Southern District of New York
15 DANIEL CHUNG
16 ELISHA KOBRE
16 Assistant United States Attorneys

17 MICHAEL SPORN
18 SCOTT MICHELMAN
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19 Attorneys for Defendant McCarthy

20 JOHN C. MERINGOLO
20 Attorney for Defendant Hough

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1 (Hearing resumed)

2 THE COURT: Are there any preliminary matters that the
3 parties wish to raise?

4 MR. RORTY: No, thank you.

5 MR. CHUNG: Not from the government.

6 THE COURT: I have one. Thinking about this last
7 evening, this Court has granted the application of
8 Mr. Michaelman and Mr. Rorty to appear pro hac vice in
9 connection with this hearing on behalf of the defendant
10 Mr. McCarthy.

11 Mr. McCarthy, I would like to hear from you that you
12 consent to their serving as counsel, advocating on your behalf
13 here during the course of this hearing. I note that you are
14 joined by the counsel who the court has appointed for you,
15 Mr. Sporn, but he is decidedly taking a backseat to the conduct
16 of this hearing.

17 So my question to you, Mr. McCarthy, is do you consent
18 to having Mr. Michaelman and Mr. Rorty represent you in
19 connection with this hearing and the conduct of this hearing?

20 DEFENDANT McCARTHY: Yes, your Honor, I do.

21 THE COURT: Yes, Mr. Sporn.

22 MR. SPORN: Before you go to the next point, the Court
23 should be aware that this was not a matter that was not
24 discussed with Mr. McCarthy. He was on board with this from
25 the beginning.

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1 THE COURT: I am confident that it was. I also
2 thought that I may have previously had this discussion with
3 Mr. McCarthy in open court, but in looking at a prior
4 transcript, it appears to me that I may not have. So I just
5 want to make it clear here on the record.

6 MR. SPORN: Thank you.

7 THE COURT: In addition, for the sake of the record,
8 Mr. Meringolo, does your client join in this application that
9 Mr. McCarthy is making?

10 MR. MERINGOLO: Yes, he does, your Honor.

11 THE COURT: I take it that if at any point during the
12 course of the hearing that you have any interest in asking a
13 question of one of the witnesses, that you will alert me to
14 that fact?

15 MR. MERINGOLO: Absolutely.

16 THE COURT: And that yesterday you had no questions
17 that you wanted to pose to any of the witnesses?

18 MR. MERINGOLO: I did not.

19 THE COURT: Very well.

20 I think that we are ready then to resume then with
21 Dr. Parrot.

22 Good morning, Doctor.

23 You may take a seat.

24 Do you understand, Dr. Parrot, that you continue to be
25 sworn as a witness under oath in this proceeding now on trial?

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1 THE WITNESS: I do.

2 THE COURT: Counsel, you may inquire.

3 MR. KOBRE: Thank you, your Honor.

4 ANDREW CHARLES PARROTT,

5 recalled as a witness by the government,

6 having been previously duly sworn, testified as follows:

7 DIRECT EXAMINATION (Continued)

8 BY MR. KOBRE:

9 Q. Dr. Parrott, have you had an opportunity to review a
10 document dated May 2001 by the United States Sentencing
11 Commission titled "Report to the Congress, MDMA Drug Offenses,
12 Explanation of Recent Guidelines Amendments"?

13 A. Yes, I have read it.

14 Q. How did you come to review that document?

15 A. You sent me the document.

16 Q. Now, I am going to read you from a portion of the document
17 titled "Health Hazards." Have you reviewed that portion of the
18 document?

19 A. Yes, I have read that section.

20 Q. There is a statement in there that says the following. It
21 says: "Finding from multiple scientific studies describing
22 symptoms of acute toxicity from MDMA use, including mental
23 status changes, hyperthermia and other symptoms associated with
24 serotonin syndrome" -- I skipped a little portion of that. Let
25 me just back up again.

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1 "A comprehensive review of the scientific literature
2 reports findings from multiple scientific studies describing
3 symptoms of acute toxicity from MDMA use, including mental
4 status changes, hyperthermia and other symptoms associated with
5 serotonin syndrome."

6 Can you comment on that statement?

7 A. I would agree with that statement.

8 Q. Does that statement refer to some of the acute effects of
9 MDMA that you talked about yesterday?

10 A. It certainly refers to some of the acute effects of MDMA
11 and related to the serotonin syndrome, yes.

12 Q. I want to take you to another statement in that same
13 section of the report. The statement says that the brain scan
14 comparison of MDMA users with non-users indicated that users
15 had a significantly reduced number of serotonin transporters
16 throughout the brain and that the magnitude of the loss was
17 associated with greater use of the drug. Do you agree with
18 that statement?

19 A. Yes, I agree with that statement.

20 Q. Could you talk briefly -- and you may have done this a
21 little bit yesterday -- but if you could just talk briefly
22 about some of the scientific literature that supports that
23 statement?

24 A. Well, there have been a number of brain imaging studies and
25 they have been reviewed by Cowan in 2007. And Cowan concluded

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1 that one of the most consistent findings of the imaging studies
2 on Ecstasy users was a reduction in serotonin transporter
3 density in the higher brain regions.

4 Q. What does that mean a reduction of serotonin brain
5 transporter density?

6 A. Serotonin cell at the base of the brain stem, the Raphe
7 nuclei, isn't damaged, the cell remains alive. However, it
8 sends very fine axon terminals to the higher brain regions.
9 And these are measured by PET scans and other imaging devices
10 in terms of the distal axon terminals. And the model is that
11 these are lost, these are damaged to a certain extent in
12 Ecstasy users and that you get a reduction of these in the
13 higher brain regions. That's also what Cowan concluded.

14 Q. Was Cowan a review paper?

15 A. Cowan was a review paper, yes.

16 Q. Can you tell us about some particular individual studies
17 that found the phenomena that you are referring to, the damage
18 to the axon?

19 A. Well, Cowan reviewed many studies until 2007 and found a
20 fairly consistent finding. But more recently, Kish -- which we
21 mentioned briefly yesterday -- has confirmed this again in
22 probably one of the best controlled studies that has been
23 published so far. It is very large study, and they have
24 controlled for many potential confounds. As they describe in
25 the paper, they tried to control for every confound they could

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1 look at and still found deficits.

2 Q. Was Kish a study involving human subjects?

3 A. Yes. It was human subjects, and I think it was two sample
4 sizes, 49 and 50. One was a control, non-users, and the other
5 was Ecstasy polydrug users.

6 Q. In the Kish study, what sort of dosages were the subjects
7 taking? What sort of dosages of MDMA had the subjects in Kish
8 taken?

9 A. Well, the Kish paper in its introduction said it aimed to
10 test an average user of Ecstasy. And the average number of
11 tablets was around about 200, but there was a range.

12 Q. When you say 200, do you mean the lifetime episodes of use?

13 A. I would have to check the paper. I know I have a figure of
14 200. I am not quite sure if these tablets were lifetime
15 episodes, I would have to check the paper for that. That is my
16 recollection, anyway.

17 Q. Was the Kish paper referring to subjects whose use of MDMA
18 you would say was fairly typical?

19 A. The Kish paper, in its introduction, aims to get, as they
20 say, an average user, so it was a range of user, but that was
21 their intention.

22 Q. Are there any particular prior neuroimaging studies similar
23 to Kish that you can tell us about?

24 A. Well, the Reneman group has undertaken studies, Sentel,
25 McCann -- they have all published studies. It is really not my

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1 area of expertise, but I have read the papers. And there seems
2 to be a fairly consistent finding that there is a reduction in
3 density of these serotonin transporters in many of these
4 studies.

5 Q. Thank you, Professor Parrott.

6 I am going to read you another statement from the
7 Sentencing Commission report that I referred to earlier, and I
8 am going to ask you to comment on it.

9 THE COURT: If you would just tell me what page you
10 are reading.

11 MR. KOBRE: Yes, your Honor. I am referring to page
12 9, right now, the last paragraph on it.

13 THE COURT: Thank you.

14 BY MR. KOBRE:

15 Q. In the third sentence of that paragraph, it says that users
16 demonstrated significant impairments in visual and verbal
17 memory.

18 A. Sorry. What paper was this, again?

19 Q. I am referring now to the Sentencing Commission report?

20 A. Sentencing Commission, sorry.

21 Q. Sure. It says that users demonstrated significant
22 impairment in visual and verbal memory. I want to ask you
23 first about verbal memory.

24 Can you tell the Court about some studies and what has
25 been found with regard to MDMA use and its effect on verbal

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1 memory?

2 A. Well, a number of studies have investigated verbal memory
3 and many of them have found deficits in Ecstasy users, so it is
4 a fairly consistent finding across many studies -- not all.

5 Q. Before maybe we turn to some of those studies, can you
6 define what is verbal memory?

7 A. Well, a typical verbal memory task would be to give
8 somebody what is called a super span task, that is a span of
9 words longer than you can normally memorize, typically, 15 or
10 16 words. So an average person might well recall 10 or so, and
11 then and you see if the Ecstasy user can also remember that
12 number or remembers more or less.

13 Q. Can you describe some of the research regarding verbal
14 memory and the effect of MDMA on verbal memory?

15 A. Well, one of the most widely used tests is the Rey Auditory
16 Verbal Learning Test, RAVLT, and this consists of giving the
17 reader a list of 16 words and then asking them to recall them.
18 Then the list is given again and they are given a second
19 recall. Then given a third time and again, often to five
20 times, and you measure how many words they recall. And,
21 typically, you get a slight increase with each repetition of
22 list.

23 Q. There was some talk yesterday about a paper by Rogers. Can
24 you describe whether Rogers investigated the effect of MDMA on
25 verbal memory?

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1 A. Sorry. Is this for Rogers review?

2 Q. That's the paper --

3 A. The meta-analysis?

4 Q. Yes. I think that's the paper that Dr. Curran referred.

5 A. Yes. There are two Rogers. There is a Rogers et al.
6 meta-analysis. So the Rogers et al. meta-analysis was
7 published in 2009 and they looked at many different studies
8 which had used the Rey Auditory Verbal Learning Tests. And I
9 think they found there were about nine studies. There was
10 quite a difference in findings across studies.

11 A couple of the studies found no indication of
12 performance impairment in the Ecstasy users, indeed, slightly
13 better performance -- it wasn't significant -- in the Ecstasy
14 users compared with controls. One of the studies, I think,
15 though, performance was very similar. And the other studies
16 spoked relative decrements and several of these studies showed
17 significant decrements.

18 Rogers et al. then undertook a meta-analysis which was
19 described by Val Curran yesterday which is basically reducing
20 all of the studies to a simple common denominator and then
21 seeing what is the average effect. When they did this, they
22 concluded that over all these different studies, there was a
23 significant decrement in the Ecstasy users compared with
24 controls.

25 Q. Does that mean that there was a decrease in the number of

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1 words that the MDMA users were able to recall?

2 A. Yes. They recalled less words.

3 Q. We heard testimony yesterday from Dr. Curran that the
4 decrease in some of the studies, the number of words that were
5 decreased, that it was relatively a mild effect. Could you
6 comment on that?

7 A. Again, there was tremendous variation between studies.
8 Some studies found small deficits. Others found larger
9 deficits. So there was variation.

10 Q. Could you describe a study that has found a large deficit,
11 what you would consider a large deficit?

12 A. Well, I can't recall which of the Rey papers found a large
13 deficit. As I say some of the studies found larger deficits.
14 I cannot remember which ones found the larger deficits.

15 Q. Are there any papers outside of the Rogers review that also
16 studied verbal memory and its effect on MDMA?

17 A. There is a very good paper by Gouzoulis-Mayfrank published
18 in the year 2000 that is in the Journal of Neurology,
19 Neurosurgery and Psychiatry, I believe. They did a very well
20 controlled study in that they had 28 Ecstasy users. And we
21 have heard already, Ecstasy users are often polydrug users.
22 And round about 24 or 25 of these also used cannabis. So they
23 then generated a matched control group of cannabis users where
24 they tried to match the use of cannabis across all
25 participants. So the cannabis user group actually had four or

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1 five people who had never taken cannabis, simply is they
2 matched as closely as possible the Ecstasy users. And then
3 they had a third group who were the clean group, the control
4 group who had never taken either cannabis or Ecstasy.

5 And they give them a German version of the Rey
6 Auditory Verbal Learning Test which is slightly different. It
7 only has 15 words and, obviously, German words, so it was not
8 included in Rogers meta-analysis. They found significant
9 deficits in the Ecstasy users compared with the cannabis users.
10 And, also, they found that the cannabis users were not impaired
11 compared with the control group. So this was really quite a
12 nice benchmark study for showing basically the effects of
13 Ecstasy rather than cannabis.

14 Q. Are there any studies -- I am looking at verbal memory in
15 Ecstasy users after a period of abstinence?

16 A. Yes. Morgan looked at verbal memory. This wasn't the Rey
17 Auditory Verbal Learning Test he used. This was a Rivermead
18 paragraph and, basically, the Rivermead task is where you are
19 given a short paragraph with round about 21 pieces of
20 information. And then you are asked to recall that, write the
21 story back down again. And then it is scored in a standard
22 format for how many items of information you recall.

23 In the Rivermead paragraph recall test, Morgan, in
24 that paper in 2002 -- this was published in the Journal of
25 Psychopharmacology, they had four groups. They had the control

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(212) 805-0300

0C7UMCC1 Parrott - direct

1 users. They had a polydrug user control group. They then had
2 a current Ecstasy user group. And they had a former Ecstasy
3 user group who had stopped using Ecstasy for at least six
4 months on an average -- the average quit time was two years.

5 And my recollection of the paragraph recall test was
6 that the controls recalled about 8.9 items; the polydrug about
7 7.5; the current Ecstasy, I think, was round about 6; and the
8 former Ecstasy users, round about 4.5 items of information. So
9 in fact their recollection of information was really quite a
10 lot higher.

11 Q. To summarize, if you compare the non-user control group
12 with the former Ecstasy user group, they were able to get about
13 half --

14 A. Probably 55 percent, 60 percent, something like that, yeah.

15 Q. And these were users who have been abstinent for how long?

16 A. I would say the criterion was six months, and the group
17 mean was two years.

18 Q. So what does that imply to you about whether the effect of
19 MDMA has some permanency?

20 A. Well, certainly that group seemed to show quite an enduring
21 deficit in their memory.

22 Q. You described just a moment ago, what you called the
23 Rivermead behavioral test?

24 A. Rivermead, yes.

25 Q. Did Rogers also perform a meta-analysis with respect to

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0C7UMCC1 Parrott - direct

1 that test of verbal memory?

2 A. Yes. Rogers does have a review 2009, and it was a similar
3 number of studies. I can't recall how many exactly, but it was
4 round about seven, eight, nine studies used for Rivermead.
5 Again, it was the meta-analysis and, again, they found a
6 variation in findings. Some studies didn't find a deficit and
7 others did.

8 In matters of meta-analysis, they did it on two
9 groups. One was the current users. And there the
10 meta-analysis, they didn't find significant effect. There was
11 lower performance in the Ecstasy users, but it didn't reach
12 significance.

13 They then did a separate analysis on the four studies
14 which had looked at former users. And that included the Morgan
15 study -- that was one study, three others were included as
16 well. In their meta-analysis, they showed that all four
17 studies showed significant impairments in the former users and
18 that the overall effect was significant.

19 Q. So what do all of these results sort of lead you to
20 conclude with regard to the effect of Ecstasy on verbal memory?

21 A. Certainly in term of the Rivermead test, it indicates the
22 memory effects are enduring.

23 Q. Professor Parrott, we have spoken about verbal memory. Can
24 you tell the Court what is prospective memory?

25 A. Prospective memory is remembering something in the future.

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0C7UMCC1 Parrott - direct

1 It is a more complex form of memory in that if you arrange to
2 meet somebody at 5 o'clock on the evening -- I think I briefly
3 described it yesterday evening. If you are meeting somebody at
4 5 o'clock and you forget to turn up, then that is a failure of
5 prospective memory.

6 Prospective memory is more complicated because it
7 involves both planning, so it is thought to involve frontal
8 aspects like remembering that at 5 o'clock you have to meet
9 somebody and then a memory component that you have to remember
10 what it is you have to do, that you have to meet such and such
11 in a particular place. And prospective memory has been studied
12 in Ecstasy users.

13 Q. Is there a consensus of scientific opinion regarding how
14 repeated use of MDMA affects a human's prospective memory?

15 A. There are several studies which have looked at this and
16 they have generally found deficits in prospective memory. The
17 first studies were by Heffernan et al. in 2001, and then a
18 study by Rendell 2007.

19 Q. Just to be clear, these studies that we are talking about
20 now, we are not talking about acute studies. Are we talking
21 about after the person is no longer on the drug?

22 A. Typically, they will have a one-week washout. That's a
23 typical description for many of these studies. That would be
24 an average for most of the research in this area. Some have a
25 shorter period, some have a longer.

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0C7UMCC1 Parrott - direct

1 THE COURT: I don't understand that term. Can you
2 explain to me what you meant when you say a one-week washout?

3 THE WITNESS: If you took Ecstasy on a Saturday, then
4 seven days later you could then be tested. And the theory is
5 that you no longer have the drug in your system but, also, that
6 you will no longer be suffering the withdrawal effects that we
7 talked about yesterday, the mid week blues, the low levels of
8 serotonin.

9 THE COURT: How long does Ecstasy remain in someone's
10 system where it would be detectable?

11 THE WITNESS: That is a complicated question because
12 it is metabolized into other drugs such as MDMA, but it is
13 generally quite a rapidly acting drug. It is fairly quite
14 rapidly metabolized, so it has peak effects for three, four
15 hours, and then the effects start to wear off and you will have
16 reducing amount of drug in your system.

17 The tail of any drug metabolism is very long, so you
18 have a peak and long tail, so you may well have small amounts
19 of drug in your system for quite a period. But in terms of
20 peak effects, that is thought to be fairly short for Ecstasy.
21 However, one crucial factor is that, as Val Curran noted
22 yesterday, you have problems days afterwards because your
23 tryptophan hydroxylase takes time to recover. So it takes a
24 while for your serotonin system to recover after taking the
25 drug. That's why you need a washout period to try to make sure

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0C7UMCC1 Parrott - direct

1 that you are not testing the recovery effects of the drug.

2 THE COURT: Thank you.

3 BY MR. KOBRE:

4 Q. In terms of prospective memory, I think your testimony was
5 that it is affected by MDMA, and you were starting to tell us
6 about some of the studies. Before we get there, which part of
7 the brain would generally be implicated in prospective memory?

8 A. The two parts of the brain are generally thought to be the
9 hippocampus which is very important to memory and also the
10 frontal lobes which are important for planning. And so it is
11 thought that prospective memory is particularly involved in
12 both functions.

13 Q. Can you tell us some of the research that has been done
14 regarding the effect of MDMA on prospective memory?

15 A. Well, Rendell has probably taken the most comprehensive
16 study. That was published in Psychopharmacology in 2007.
17 Rendell et al. And they had a virtual game board task.

18 Basically, Rendell is not really psychopharmacology.
19 He comes from a prospective memory background, so he is more of
20 a cognitive psychologist. And he developed this game board
21 which consists of throwing dice and going round the board five
22 times to represent five days. And as you go around the board,
23 you have to remember to do certain things and respond to
24 certain cues. So you have a cue on the board which you will
25 pass. As you pass that cue, you know that you have to do

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(212) 805-0300

0C7UMCC1 Parrott - direct

1 something. So the question is, do you remember to do that
2 thing when you pass the cue. So the board doesn't tell you
3 what to do; it just gives you the cue for doing that action.
4 So it may well be that you pass cues and fail to do the task.
5 So that's a failure of prospective memory.

6 They had three groups. They had non-user controls.
7 They had what they call light intermittent Ecstasy users. And
8 these were people that typically used once a month or less, so
9 it is not very frequent users. And they had a second group who
10 typically use twice a month or more, so they were seen as more
11 the moderate to heavy to regular users.

12 One of the benefits of this task is they generated
13 lots of prospective memory scores, which means it was a very
14 sensitive test. When they analyzed the data, they found that
15 the low intermittent Ecstasy group was significantly impaired
16 compared with the non-user controls. And then when they looked
17 at heavy Ecstasy users, they were significantly impaired when
18 compared to the controls and to the intermittent group. So
19 they had very nice dose-related data.

20 Q. Just to clarify, these were effects were observed off
21 drugs, after a period of some days?

22 A. In this particular study, because Rendell was not a
23 psychopharmacologist, their particular criterion for abstinence
24 wasn't a good one. I think they said they had to be drug free
25 for either one day or two days. I can't remember. And they

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(212) 805-0300

0C7UMCC1 Parrott - direct

1 didn't differentiate between drugs. Many studies say you have
2 to be free of alcohol for one day or cannabis for two days, but
3 free of Ecstasy for seven days.

4 This particular study, because they were not
5 particularly sophisticated psychopharmacologists, they had not
6 done that. So that is a potential criticism of the study,
7 however, if you look at the user pattern of the Ecstasy users,
8 if they are using once a month or less, it is unlikely that
9 they would have taken the drug in the days afterwards.

10 Q. I think you described some other research also regarding
11 prospective memory, other studies that were done?

12 A. There have been other studies Heffernan et al. has tested
13 this. And they found it both on questionnaires, so if you
14 asked Ecstasy users do you suffer from memory problems, what
15 you tend to find is a significant increase in reports of
16 prospective memory deficits in the Ecstasy uses. Heffernan et
17 al. also used a video game. And in that study they also
18 reported deficits.

19 Q. Do the finding you referred to in Rendell and Heffernan,
20 what do those sort of findings imply for functioning in every
21 day life?

22 A. Well, to give you one practical example, I actually
23 supervise lots of students doing projects. And many years ago
24 when we first started out, my research student said to me, we
25 are having problems. The controls are turning up for the

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1 appointments and the Ecstasy users keep on missing
2 appointments.

3 I said, well, it is just because they lead chaotic
4 lifestyles or something like that. And I didn't think much
5 more about that. But then when the Heffernan papers came
6 through, first reporting prospective memory deficits in Ecstasy
7 users, the penny dropped, and I suddenly realized why the
8 Ecstasy users in particular were missing their appointments.

9 So now when I supervise my project students, I get
10 them to phone up, I get them to a mobile phone number and I say
11 to them, phone them up before the test to make sure that they
12 are going to turn up to save wasting time.

13 Q. Thank you.

14 What is executive functioning?

15 A. Executive functioning is thought to be one of the highest
16 aspects of human activity. It is planning, it is strategic.
17 It is problem solving -- all of these higher functions.

18 Q. Is there a consensus of scientific opinion regarding how
19 repeated use of MDMA affects an individual's executive
20 functioning ability?

21 A. Yes. There have been a number of studies conducted in this
22 area, and this is now thought to be the other area, in addition
23 to memory, where Ecstasy users often report impairments.

24 Q. Can you describe some of the research regarding executive
25 functioning?

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1 A. Well, one of the first studies was undertaken by Michelle
2 Wareing in the British Journal Psychology published in 2000.
3 And she found a significant deficit in a task which is a
4 strange task to describe. It sounds very simple, but it is
5 actually quite sensitive. And it is called random letter
6 generation. So you are asked every few seconds to generate a
7 letter. And then on a regular period you generate another
8 letter. And you are not supposed to repeat letters or do it in
9 strings or have consecutive letters. And it is actually quite
10 difficult. Many people can do it at a rate of one letter every
11 four seconds, but the fun starts when you start giving the task
12 more rapidly, the two seconds and one second. Wareing did this
13 in their study, and they found that the Ecstasy users were
14 impaired and some of them found difficulty with the task.
15 Q. Just to clarify, again, we are talking about an off drug
16 observation?
17 A. These were Ecstasy users off of drugs, yes.
18 Q. Have those findings of Wareing regarding executive
19 functioning, have they been confirmed in later studies?
20 A. Well, various executive functions -- do you want me to talk
21 about another type of executive function?
22 Q. If they relate to a later study -- later after Wareing, I
23 believe you mentioned was in 2000?
24 A. Right, yes. My recollection of Rogers review is this is
25 one of the areas they looked at. And, again, my recollection

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1 is they did find executive frontal problems were significantly
2 impaired over a range of studies. Again, there is variation in
3 findings but, on average, they found a deficit.

4 Q. I think you mentioned before that executive functioning is
5 somehow related to logical reasoning?

6 A. That is right.

7 Q. Can you describe some of the research about how MDMA
8 affects a user's ability to engage in logical reasoning?

9 A. Well, Fisk et al. published a paper in 2004 that is in the
10 Journal of Psychopharmacology, and they looked to Ecstasy users
11 versus controls. And they gave what is called an Aristotelian
12 syllogism test. It is along the lines of if A -- some of A are
13 B and some of B are C, are all A, B or all A, C -- sorry, it is
14 not very accurate, but it is along those lines and you have a
15 series of these problems.

16 Now, on this particular study, they trained all of the
17 participants on this logical problem solving beforehand and
18 then they gave them on the basic problem solving, and then they
19 gave them tests to see how good they were at this particular
20 problem solving procedure. And they found a significant
21 deficit in the Ecstasy users.

22 One problem was, the deficits in this particular study
23 were not just related to MDMA; they were related to other drugs
24 as well, so they couldn't offer firm conclusion about the role
25 of other drugs, although when they analyzed it, they said that

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1 the strongest relationship was with Ecstasy.

2 Q. Did they analyze the data using statistical methods?

3 A. Yes.

4 Q. Were they able to sort of using statistical methods control
5 for use of other drugs?

6 A. As I said, what they found in this particular study was
7 this particular logical reasoning was associated not only with
8 Ecstasy but other drugs such as cocaine and amphetamine.

9 Q. Professor Parrott, so far we have talked about verbal
10 memory, prospective memory, executive functioning, logical
11 reasoning. There is one sort of area further in this section
12 that I would like to cover which is social intelligence, and if
13 you could tell the Court what that is?

14 A. There is a paper by Rey et al. that is published in Journal
15 of Psychopharmacology in 2006 and they tested both executive
16 functions in Ecstasy users, and they gave what is called a
17 social intelligence questionnaire, which is a questionnaire
18 developed by other researchers. And it looks at subtle
19 processes which underlie social interactions such as, do you
20 find it easy to understand other people's emotions -- that sort
21 of quotation is the sort of question covered in that
22 questionnaire.

23 What they found was that the Ecstasy users reported
24 deficits in that questionnaire. And when they controlled for
25 other drug use, they found that the deficits remained after

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1 controlling for these other drugs.

2 Q. So was it their conclusion that the deficits were related
3 to Ecstasy?

4 A. In their theoretical discussion, they hypothesized that it
5 may well be an aspect of this higher planning, higher executive
6 processing that was the hypothetical explanation for their
7 finding.

8 Q. Just returning now to the Sentencing Commission report on
9 page 9, and the statement of the report that Ecstasy users
10 demonstrated significant impairments in visual and verbal
11 memory, do these findings that you have talked about until now,
12 do they speak to that statement?

13 A. Yes. In recent studies there have been a number of studies
14 which have confirmed these sorts of memory deficits.

15 Q. I want to read you another statement from the Sentencing
16 Commission report. And now I am referring again on page 9 to
17 the last line on that page and it talks about a conclusion
18 among reports that MDMA use may impair a subsystem termed
19 working memory. Could you comment on that statement?

20 A. Well, again, working memory was what I talked about with
21 Michelle Wareing related to executive functioning, and so
22 working memory does seem to be impaired.

23 Q. And then referring to the top line on page 10 of the
24 Sentencing Commission report: "It talks about the fact that
25 these deficits in working memory, this form of disturbance it

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1 calls it, is likely related to the well recognized neurotoxic
2 potential of Ecstasy." Do you agree with that statement?

3 A. I'm sorry. Could you read that again?

4 Q. I will read you the entire statement which is: "It talks
5 about a conclusion among some groups that MDMA may impair a
6 subsystem termed working memory and that this form of
7 disturbance is likely related to the well recognized neurotoxic
8 potential of Ecstasy." Could you comment on that?

9 A. Certainly memory is associated with deficits -- the Kish et
10 al. study showed that there was an association between the
11 serotonin transporter loss and then memory impairments. I am
12 not sure that the Kish et al. had a working memory study in
13 their report. I will have to check on that. But certainly
14 many groups found working memory deficits and verbal memory
15 deficits. Certainly many groups have talked about it in
16 theoretical terms as reflecting this memory loss.

17 Q. Is MDMA addictive?

18 A. It is generally perceived as non-addictive in certain light
19 initial users it displayed very minimal addictive properties,
20 so it is probably one of the least addictive drugs, however, if
21 you look at heavy users, they start to display many of the
22 classic signs of drug addiction or drug dependence.

23 Q. Can you describe some of the studies that have been done
24 with regard to dependence on MDMA.

25 A. Well, Topp et al. published an Australian government in

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1 19987 where they concluded that there was a syndrome of Ecstasy
2 dependence, but it was untypical of other drugs. So, again, it
3 was only showed in a minority of users.

4 And this was developed in later reports by Bruno et
5 al. published in the Journal of Neuropsychology in 2008. They
6 interviewed or surveyed -- I can't remember if it is a
7 questionnaire or an interview -- about 1,500 people and they
8 found 20 percent of the sample reported a symptom severity
9 dependence scale score of 4 or more which they took to indicate
10 MDMA dependence.

11 They then split the sample into two subgroups, the 80
12 percent who didn't report symptoms of this criterion and 20
13 percent who did. And they found that the dependence was
14 associated with greater lifetime use and greater intensity of
15 use. So, for instance, were people taking the drug more than
16 once a week, and if they were, that was associated with
17 dependence.

18 Q. So in looking at those studies is there a significant --

19 A. If I can correct that, the actual score on questionnaire
20 was in the past six months have you taken Ecstasy more than
21 once a week. So those people that tick yes to that were more
22 highly proportioned in the dependence group.

23 Q. In looking at those studies, is dependence a significant
24 issue in MDMA?

25 A. Once people move up the usage scale, then they start to

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1 develop more of the classic signs of dependence.

2 One of the reasons Ecstasy is far less dependent
3 producing than other drugs is its long time scale. With drugs
4 like cocaine, you can take cocaine quite frequently and have
5 effective hits. And this is less so than MDMA where you need
6 this washout period to take it again.

7 So there is a study by Hopper et al. published in
8 2006. I cannot remember the journal, but it was one of the
9 standard peer review journals, and they looked at symptoms of
10 craving for Ecstasy. And they gave people a little
11 microcomputer to keep on them. And this computer beeped at
12 certain times and they had to report whether they were craving
13 for Ecstasy.

14 And what this group found was minimal craving
15 throughout most of the study. So when people beeped most of
16 the time, they had no Ecstasy craving, however, what they found
17 was, craving started to develop on the afternoon of the evening
18 when they are planning to take the drug. And the craving then
19 built up in the few hours before intended use.

20 So it is a very unusual drug, but it does have some
21 aspects of dependency, but it is very unlike the classic drugs.

22 Q. But there are users who experience dependency on the drug?

23 A. Once people become very heavy users, they can display quite
24 marked dependency and very repeated use.

25 Q. Is there data on the percentage of people who become

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1 heavier users?

2 A. To that level of extreme dependence, I think it is probably
3 quite unusual. I don't know of any percentage figures.

4 Q. Professor Parrott, I want to read you another statement
5 from the Sentencing Commission report.

6 I am now referring to page 10, the first full
7 paragraph and it states: "That another point of controversy
8 surrounding the MDMA research literature is whether a loss of
9 the serotonin sites and the corresponding impairment is
10 permanent."

11 I want you, if you can, to comment on the question of
12 whether the functional aspects -- that we have been discussing
13 earlier, the impairments to memory -- whether there is any
14 research discussing whether those are permanent?

15 A. Well, this is still very much a wide open question, but the
16 Morgan study I quoted earlier is one of the very few studies
17 which has looked at this. And certainly they have data on the
18 former users that suggest that their memory impairments were
19 enduring, but that obviously needs to be developed in further
20 studies.

21 There is another by paper by Zakzanis published in
22 2006. I can't remember the journal offhand but, again, it is
23 very small study and they were following up Ecstasy users over
24 time. And what they found was that those Ecstasy users who
25 carried on using tended to continue to develop memory problems,

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1 whereas those that quit, they either remained or the memory
2 performance improved.

3 So there's variation in findings. It is really far,
4 far too early. We haven't got the adequate data to answer that
5 question.

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(Continued on next page)

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0C74MCC2 Parrott - direct

1 BY MR. KOBRE:

2 Q. Would it be fair to say that there is data in both
3 directions?

4 A. Yes, Morgan would be in one direction; Zakzanis would
5 indicate some recovery, yes.

6 Q. Did Zakzanis indicate whether the recovery actually brought
7 the users back to baseline?

8 A. My recollection of the scores was the scores often moved
9 towards the baseline. I don't seem to recall that they reached
10 the score they had earlier. I would have to check the paper.

11 Q. Mr. Parrott, have there been any studies regarding the
12 chronic effects of MDMA upon the human immune system?

13 A. This is an area of interest. The animal literature shows
14 that MDMA is a very powerful suppressant on the immune system.
15 Connors in 2004 published a review in this area. Most of the
16 review was focused on the animal literature. It showed that
17 MDMA didn't reduce the immune system. They then quoted some
18 studies. In the Connors review they looked at some studies by
19 an Italian group Pacifici et al. they published a series of
20 studies looking at immuno reactions in Ecstasy users. They
21 found impairments on some of these measures.

22 Q. What sort of impairments, what were they looking at?

23 A. They took blood samples, like lymphocytes, white blood
24 cells, natural killer cells. These were important for fighting
25 natural killer cells, I suppose an accurate name. Their job is

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0C74MCC2 Parrott - direct

1 to attack and kill foreign substances. You also got
2 neutrophils which they also investigated. They found that
3 there was a reduction in these natural killer cells in Ecstasy
4 users.

5 Q. Were those studies performed while the subjects were on
6 MDMA?

7 A. These were prospective studies followed over time. I can't
8 recall if they are absent users or former users. The blood
9 samples were taken off-drug.

10 Q. Off-drug?

11 A. Yes, off-drug. They also cited our paper which is perhaps
12 the only humans paper on this where we asked users, have you
13 suffered coughs and colds. What we found was a dose-related
14 instance. This a study we published in 2002 in human
15 psychopharmacology. This is an Internet survey of several
16 hundred Ecstasy users. The heavier Ecstasy user group reported
17 significantly more instance of this problem then the novice
18 users with the modest group, intermediate. I think it was 35
19 percent of the heavy group reported this problem, but that was
20 just self-reports.

21 Q. Can you tell the court what is cortisol?

22 A. Cortisol is an important neurohormone.

23 Q. Have there been any studies, we talked about the effects of
24 MDMA on serotonin, have there been any studies regarding the
25 effects of MDMA on human cortisol levels?

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1 A. Basically if you administer an acute dose of MDMA in the
2 laboratory, you will get an increase in many hormones for a few
3 hours. Cortisol is one of those. Daumann and Verkes published
4 a review in 2006 and they reviewed 12 studies which looked at
5 the effects of acute doses of MDMA upon cortisol. They showed
6 that in 11 of those studies you got an increase in cortisol.
7 The 12th study didn't find an increase but that was of a low
8 dose of MDMA.

9 So, in laboratory it certainly induces a consistent
10 increase in cortisol. We have done two studies where we looked
11 at cortisol in recreational users. These were users who went
12 clubbing on Ecstasy one weekend; on the other weekend, they
13 agreed to go clubbing to the same club with the same friends,
14 same group of friends, same club, same day, but not take
15 Ecstasy. We published that study in 2008 in the Journal of
16 Neuropsychobiology. Interesting, the range of variables, and
17 one of the most surprising findings we found was this increase
18 in cortisol which was 800 percent. I talked to neurohormone
19 people and they said this increase in cortisol is really quite
20 a dramatic increase.

21 Q. You said 800 percent?

22 A. 800 percent.

23 Q. Describe what sort of long-term health effects can result
24 from an increase of cortisol to that degree?

25 A. Cortisol is known to be involved in many functions,

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OC74MCC2 Parrott - direct

1 cognitive. Basically cortisol, if I can digress slightly, is
2 important for homeostasis. Homeostasis is our normal bodily
3 control. In the normal body we have a cortisol, an endogenous
4 cortisol rhythm.

5 So a few hours before we wake our cortisol system
6 kicks into action and we start about 5, 6 in the morning to
7 have an increase in cortisol. So by the time we wake at 7:00,
8 the cortisol system is already getting us ready for action. It
9 peaks after one or two hours, then it tails off and remains
10 stable for the rest of the day. So cortisol is important for
11 getting us up, getting us awake, getting us alert in the
12 morning, then it remains stable over time. So that's
13 endogenous rhythm.

14 The other side of cortisol is what's called reactive
15 homeostasis. This is when we have stressors to the bodily
16 systems which we have to face. If we face a stressful
17 situation like walking down a dark alley and you are afraid or
18 the dust bin is knocked over and you have this fear reaction,
19 then your cortisol reaction will kick into gear. It also
20 occurs during marathon running, endurance sports, high
21 temperature. It's thought to be a bodily reaction to coping
22 with stress.

23 Q. Repeated stresses of this nature, what kind of long-term
24 health effects if any could there be?

25 A. When cortisol is released from your body, it stimulates

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Parrott - direct

1 what's called a symphoneumatic action, so this is activity in
2 the symphosympathetic nervous system which is the autonomic
3 nervous system responsible for being active and alert. It's
4 thought that we need a balance between sympathetic activity and
5 parasympathetic activity because parasympathetic activity is
6 the opposite and that needs bodily repair. We repair muscles
7 during relaxation. When we are in the couch potato mode, our
8 body is repairing itself. When we are in the sympathetic mode,
9 then the body is being stressed.

10 One of the theories of cortisol is it's involved in
11 stress. Hans Sile first wrote about this in 1951. Stress is
12 essentially a physical reaction. It's where the body is having
13 to cope with demands about above the normal. So the theory is
14 if we are having lots of stress, that's bad for us in the
15 long-term. So the theory is that MDMA is inducing in regular
16 Ecstasy users regular periods of bodily stress and these may
17 well be related to the long-term effects of the drug.

18 If I can add to that, Connors in his review said that
19 MDMA can be regarded as a chemical stressor upon the immune
20 system. That's a direct quote from his 2004 review.

21 Q. You mentioned that with respect to some of the cognitive
22 studies there was some variation in findings. Can you tell the
23 court, since 2001 have there been any studies or reviews done
24 to explain these variations in findings?

25 A. I missed that question.

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1 Q. When you were talking earlier about some of the cognitive
2 effects of MDMA, you mentioned there was some variation in
3 findings, some papers had variation in findings. Have there
4 been any studies since 2001 to explain these variations in
5 findings?

6 A. In 2006 I published a review paper because I was
7 particularly interested in the variation findings, so in that
8 review paper --

9 Q. Is that one of the six papers --

10 A. Yes.

11 Q. -- that were submitted to the court?

12 A. Yes. I was particularly interested in why there was such a
13 variation in findings, as other people have testified in some
14 studies you don't get deficits, in other studies you do. In
15 this review I attempted to look at the factors trying to
16 explain this. I found several factors.

17 Q. Tell us what some of the factors were?

18 A. One important factor was acute dosage, so those that have a
19 large acute dose tend to have more problems in days afterwards
20 than a lower initial dose. So acute dosage is one factor. A
21 second very crucial factor is cumulative, a lifetime dose.
22 Many studies who test quite light Ecstasy users don't find
23 deficits; those who test heavy users do find deficits.

24 Another is the function being assessed. In terms of
25 cognition, we know that certain aspects of cognition are

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1 adversely affected, particularly memory, frontal planning
2 tasks. Other aspects like system tension tasks tend not to be
3 impaired. Another crucial factor is polydrug use. This has
4 been an enduring question in the literature for many years now.
5 Since before 2001 people were talking about the effects of
6 cannabis and also other stimulants.

7 So in that paper, I looked at this in detail. I
8 showed that in some studies of Ecstasy and cannabis users,
9 cannabis was the main drug responsible for the deficits. Then
10 in another group of studies of cannabis and Ecstasy users,
11 Ecstasy was associated with the deficits but not cannabis.
12 Then in another bunch of studies, because there were probably
13 30, 40 of these studies, it was both drugs.

14 Q. How do you reconcile those studies?

15 A. I looked at the studies and tried to tease out what factors
16 were there. One of the key factors was probably the relative
17 use of each drug.

18 Q. What do you mean by that?

19 A. How much, if you were a heavy user of both drugs, a light
20 user of one drug and a heavy user of the other drug. For
21 example, Croft et al., they published the first study in 2001
22 shock that in Ecstasy cannabis users, the deficits were related
23 to cannabis and not Ecstasy. Their users of cannabis were
24 10,000 times lifetime, whereas the use of Ecstasy was 40.

25 Croft et al. published another study in the same year,

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1 2001, I think it was on a psychophysiological measure. There
2 the Ecstasy users used an average 283 times, although I stand
3 corrected on that, the use of Ecstasy, use of cannabis was I
4 recall I think 2.2 joints a week, again I stand corrected.
5 Anyway it was light use of cannabis versus a lot heavier use of
6 Ecstasy. In that study, they found the deficits related to
7 Ecstasy rather than cannabis.

8 Q. Just to sum up, there are several factors that can explain
9 the variation in the studies and one of them is, with respect
10 to polydrug use, the relative use of the various drugs?

11 A. That's right. I also looked at the co-effects of
12 stimulants and there are a number of potential confounds, and
13 again, I found a variation in findings. In some studies they
14 were important confounds. I think I mentioned the Fisk study
15 in physiological reasoning. There the other stimulant drugs
16 were crucial confounds. In other reports, they looked at this
17 and found they were not confounds.

18 If I can cite one of those studies, Fox et al., 2002.
19 She was my research student. She did a study where she matched
20 the Ecstasy users and cannabis users, sorry, she had Ecstasy
21 users who were also cannabis users. The control group was
22 quite nicely matched on cannabis use. She found deficits
23 related to the Ecstasy, so she controlled for cannabis in the
24 design. She then also looked at the co-effects of other drugs
25 such as amphetamine and cocaine because the Ecstasy users were

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1 using those drugs. She showed that the deficits remained after
2 controlling for those potential confounds.

3 Q. After looking at all these factors what does your 2006
4 paper tell us about MDMA and how it affects?

5 A. The main conclusion is it was complex. Do you want me to
6 elaborate?

7 Q. Briefly.

8 A. In study after study, MDMA has been shown to be associated
9 with various tremendous variation in findings. Some studies
10 shows co-influence of other drugs because all these drugs are
11 powerful.

12 Q. Are you familiar with the study by David Nutt in 2010
13 titled Drug Harms In the U.K, a Multi Criteria Decision
14 Analysis?

15 A. Yes.

16 Q. Do you agree with the result of that paper?

17 A. No.

18 Q. Why not? First talk about methodology.

19 A. Can I talk about it in relation to his 2007 paper as well
20 or not, just 2010.

21 Q. Start with 2010.

22 A. David Nutt concludes that alcohol is the most damaging
23 drug. I agree. In my 2004 textbook, Understanding Drugs and
24 Behavior, in the chapter on alcohol, I say that alcohol is the
25 most damaging drug known to mankind. So if we are taking the

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0C74MCC2

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1 amount of damage caused to humans by drugs, alcohol is
2 definitely number 1. But what Nutt seems to be confusing in
3 this paper is overall damage to society and relative damage by
4 a drug. So, I read in a newspaper article by Nutt, who was
5 asked to comment about this review, he said even if only 10
6 percent of alcohol drinkers have problems, that's still an
7 enormous cost to society.
8 So Nutt seems to be suggesting that 90 percent of
9 alcohol use can be OK without causing particular problems. So
10 only 10 percent of alcohol users are suffering problems. So,
11 in his paper, he doesn't seem to be talking about effects of
12 drugs; he seems to be talking about the effects to society.
13 There I agree alcohol is high. But he then talks about drugs
14 and their relative harm. He says alcohol is therefore one of
15 the most harmful drugs. It's not. It's actually one of the
16 safest drugs. If you look around this room, I guess most of us
17 are probably regular alcohol drinkers. I guess most of us have
18 been drinking alcohol 30, 40 years. We can probably drink
19 alcohol for another 20, 30 years. Most of us in this room
20 won't be adversely affected; 10 percent may well be. But it's
21 relatively a benign and social drug.
22 Q. Can the same be said for MDMA?
23 A. Certainly not. Nor for cocaine, nor for cannabis, nor for
24 methadone. He puts methadone down as low. He puts CAT,
25 which is cathinone, down as a drug of low harm. He has

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1 confused overall harm for society versus the actual specific
2 effects of a particular drug.

3 Q. Does Nutt make any claims about MDMA that you wish to
4 comment on?

5 A. In his 2007 paper, he compared MDMA with various other
6 drugs. He said that MDMA was the 18th drug on the list of harm
7 for 20 drugs in all. To reach that conclusion, he rated every
8 drug on 9 harm scales. To take one example of those scales,
9 one was a relative pleasure scale. So every scale was given a
10 score from zero to 3.0. Nutt gave heroin a maximum pleasure
11 score of 3.0. He gave smoking a cigarette a pleasure score of
12 1.9 I seem to recall. And the pleasure score for MDMA, I think
13 was 1.6. But again these figures may be wrong.

14 Certainly, Nutt gave a lower pleasure score for MDMA
15 than smoking a cigarette which to my mind is amazing, but it
16 was important, in that the high score, on the pleasure score,
17 Nutt recognized that the most pleasurable drugs, like cocaine,
18 heroin, methamphetamine, are most damaging. So a high score in
19 pleasure was taken to add to the overall harm score. He seemed
20 to have artificially given MDMA a very surprisingly low
21 pleasure score which contributes to its low harm potential.

22 Another question he asked about was injection
23 potential. Again he said opiates and cocaine 3.0. MDMA, he
24 gave a score of zero. Yet there are two or three papers
25 documenting MDMA injections in Ecstasy users. So MDMA should

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1 have had a higher score from zero. But again, it contributed
2 to the artificially low score.

3 Q. The 2010 paper by Nutt, do you agree with that paper?

4 A. No.

5 Q. Are you familiar with the summaries of testimony that were
6 provided for the defense?

7 A. I have read those, yes.

8 Q. I will read some statements from those summaries of
9 testimony. I am going to ask you whether you agree or disagree
10 and just to comment. This from the summary of Dr. Curran,
11 proposed summary of testimony of Dr. Curran. It says here,
12 according to the best recent studies of the effects of MDMA in
13 humans, the drug's effects are relatively mild and not
14 permanent. Do you agree or disagree?

15 A. No. I disagree.

16 Q. It further states in the summary of Dr. Curran's proposed
17 testimony that the drug, while the drug results in impairment
18 of human users' verbal memory, the drug's effects wear off over
19 time and deficits in brain chemistry do not persist?

20 A. Again, I disagree.

21 Q. It further says in the summary of Dr. Curran's testimony
22 that current studies suggest that much of what was in the
23 report, the sentencing report, assumed to be lasting brain
24 damage is reversible temporary impairment?

25 A. Again, I don't see, it's a very open question as to how

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0C74MCC2 Parrott - direct

1 enduring it is. It's very difficult to answer that.

2 Q. Dr. Curran's summary of proposed testimony concludes that a
3 reasonable scientist familiar with the research today could not
4 reach the same overall conclusion as the 2001 report with
5 regard to its assessment of the harms of MDMA. Do you agree
6 with that?

7 A. No, I don't. I have organized a number of conferences on
8 MDMA in recent years and nearly every paper is presenting
9 deficits. These were all by reputable scientists.

10 Q. I am going to Dr. Halpern's proposed testimony as related
11 in the summary of testimony. It says here that Dr. Halpern's
12 proposed testimony would be that recent prospective studies on
13 humans have not found significant changes in serotonin systems
14 over time or evidence of permanent damage.

15 A. I disagree. I think the Kish study is a very good
16 indication of damage. As to the question of permanence, that's
17 still difficult to answer.

18 Q. Dr. Halpern's proposed testimony also says that, it takes
19 issue with the report, the sentencing submission report
20 statement that MDMA produces cognitive impairment and it says
21 here that recent studies show, according to Dr. Halpern, that
22 verbal problems are less associated with Ecstasy use than with
23 other preexisting factors.

24 A. I don't agree with that.

25 MR. KOBRE: One moment, your Honor.
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1 THE COURT: Take your time.

2 (Pause)

3 MR. KOBRE: Nothing further, your Honor.

4 THE COURT: Cross-examination.

5 THE WITNESS: Your Honor.

6 THE COURT: We are going to take a short recess right
7 now for a few minutes. You may step down. We will reconvene
8 in about five minutes.

9 (Recess)

10 THE COURT: Cross-examination, Mr. Michelman.

11 MR. MICHELMAN: Thank you, your Honor.

12 CROSS EXAMINATION

13 BY MR. MICHELMAN:

14 Q. Do you agree that MDMA is less harmful than cocaine?

15 A. No.

16 Q. But you wrote that in 2009 and again in 2010, didn't you?

17 A. Overall, if you combine crack cocaine and cocaine, crack
18 cocaine is more damaging, nasal cocaine so less damaging, so it
19 depends if you are combining the two.

20 Q. Just taking powder cocaine then, you are saying it's more
21 harmful than powder cocaine?

22 A. It's difficult, it's even-ish. Cocaine is worse on
23 addiction and MDMA is worse on energetic-related damage.

24 Q. We discussed the David Nutt study In Atlanta from 2007.

25 You had a paper published by Addiction Today called Myth

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1 Busters in which you critiqued David Nutt's article?

2 A. It wasn't my title. I wrote the article. The
3 journalist --

4 Q. I won't hold you to the title but I would like to hold you
5 to this quote. One of the things you do in Myth Busters is you
6 rescore the drugs that Dr. Nutt considered and you rescored
7 them using what you term the revised scores based on the
8 empirical literature?

9 A. Right.

10 Q. In David Nutt's original study, the 2007 study, he rated
11 cocaine the second most harmful out of the group of 20?

12 A. Right.

13 Q. He rated MDMA 18th, yes or no?

14 A. Yes.

15 Q. You write with revised scores based on empirical
16 literature, MDMA becomes the fifth most harmful drug. It's
17 still below cocaine?

18 A. Yes.

19 Q. Just to confirm that, you wrote in 2009, also discussing
20 Nutt, in response to BBC journalist Mark Easton in Addiction
21 Today, when I rescaled these scores using scientific data, then
22 MDMA emerged as the fifth most harmful drug on this list, lower
23 than heroin and cocaine. I will stop there. You go on to
24 discuss other Class A drugs.

25 A. That's correct.

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- 1 Q. So then you would agree that MDMA is less harmful than
2 cocaine?
3 A. Than overall cocaine, yes.
4 Q. You agree generally that MDMA is not addictive?
5 A. No, I said it has addiction potential.
6 Q. Potential, but actually I think you said it was one of the
7 least addictive drugs?
8 A. Yes.
9 Q. In fact, you began by saying it was not addictive then you
10 discussed some ways in which it might theoretically possibly be
11 addictive?
12 A. As I explained earlier, yes.
13 Q. You noted some dependence based on study in which the
14 question was asked whether someone had taken Ecstasy more than
15 once a month?
16 A. I am confused by that question.
17 Q. One of the studies you cited in support of a possibility of
18 addiction, asked the question whether the users had taken it
19 more than once a month, is that correct?
20 A. I am not sure which study you are referring to.
21 Q. I was reading my notes from your cross-examination. Do you
22 believe that taking Ecstasy more than once a month is
23 indicative of addiction?
24 A. I don't remember saying that in my testimony. I remember
25 saying that those who scored high on the dependence scales

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1 score, 20 percent of dependence users reported that they took
2 Ecstasy more than once a week in the previous six months.

3 Q. But your overall conclusion is that it's not addictive but
4 it has a potential for addiction?

5 A. It's not addictive in light novice users. Once people up
6 the usage and they became heavy users, then they show
7 dependence.

8 Q. Let's talk about the heavy user. I noticed throughout your
9 testimony you broke down, you broke users down between heavy
10 and more light or moderate users, right?

11 A. Yes.

12 Q. Now, wouldn't we expect to see more damage from any drug if
13 used heavily?

14 A. Yes.

15 Q. Wouldn't we expect to see more damage from any medication,
16 even a prescription medication if used heavily?

17 A. If it's a safe medication, hopefully not.

18 Q. Would you agree that most substances one could overuse them
19 to the point that it would become dangerous?

20 A. I am sure we could.

21 Q. Even drugs that would be harmless or practically harmless
22 in lower moderate doses?

23 A. I am sorry, I am lost again, a bit lost here.

24 Q. You would agree that heavy doses can be toxic or harmful
25 even for substances that are not harmful if taken in a low or

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1 moderate dose?

2 A. I am sure that's true of many substances.

3 Q. We spoke a lot about confounds and controlling for key
4 variables?

5 A. Right.

6 Q. One of the confounds you noted that was important to
7 control for in the MDMA context is the use of multiple drugs
8 which we also referred to as polydrug?

9 A. Correct.

10 Q. Is it also important to control for preexisting conditions
11 or family history of subjects?

12 A. It depends on the study. It depends what you are
13 investigating.

14 Q. Can you elaborate on that.

15 A. If you are looking at how drugs affect people with
16 problems, then you need to include them. A drug may well make
17 people with problems worse.

18 Q. If you want to rule out that the drug has caused a problem,
19 you need to control for the possibility of a preexisting
20 problem?

21 A. If that's what you are investigating, yes, you would often
22 do that.

23 Q. Wouldn't you always want to do that?

24 A. Well, if you are looking, that's an example of is MDMA
25 causing depression. You could look at two studies, one which

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1 looked at Ecstasy users who had no depression, such as McCann
2 does. They screen out people with problems, with any problems.
3 Then they found that they did develop depression. You might be
4 interested in how MDMA may be effecting depression with people
5 with clinical problems in which case you would include them.

6 Q. Unless you are investigating the effects on people with
7 preexisting problems, you would try to exclude for the
8 preexisting problems?

9 A. As I said it depends upon the study, yes.

10 Q. Would you also want to control for bias in the selection of
11 the subjects?

12 A. Yes.

13 Q. I assume the best way to study effects on humans is to
14 study, to perform MDMA studies on humans themselves; would you
15 agree with that?

16 A. I guess so, yes.

17 Q. Could you tell us in your own words what a prospective
18 study is?

19 A. A prospective study is following up people over time.

20 Q. Is that generally considered one of the better methods to
21 discover the effects of a drug?

22 A. Some people believe prospective studies are the best. I am
23 great believer in cross-sectional. Generally it's seen as a
24 better standard, yes, prospective, for answering different
25 questions, but in many instances, yes.

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1 Q. You would agree that the NextC study is a prospective
2 study?

3 A. That's right.

4 Q. That would be particularly valuable in studying the harms
5 of MDMA?

6 A. Yes.

7 Q. Is MDMA safe in your view to use in therapeutic studies to
8 investigate its possible benefits for medicinal purposes?

9 A. Probably but inadvisable.

10 Q. It's not a good idea?

11 A. I wrote a paper on this in 2007 where I discussed the pros
12 and cons. My conclusion was it's probably not advisable.

13 Q. I would like to clarify a term we have been using
14 throughout the day, actually throughout yesterday, the word
15 acute. Describe what we mean scientifically when we talk about
16 an acute effect.

17 A. An immediate effect. In MDMA terms, it's a few hours after
18 taking.

19 Q. Acute doesn't mean serious, necessarily, just immediate?

20 A. Sorry?

21 Q. Acute doesn't speak to the severity of an effect, just the
22 fact that it's immediate?

23 A. It's time-related, yes.

24 Q. I would like to talk about the sources that you submitted
25 to the court in advance of this hearing in support of your

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- 1 testimony. Obviously you referred to a great many sources
2 during the course of your testimony. But you submitted six to
3 the court in advance. These were your own study from 2001,
4 Human Pharmacology of Ecstasy, excuse me, Human
5 Psychopharmacology of Ecstasy, the Jansen study, Ecstasy MDMA
6 Dependence, the Topp study from 1999, Ecstasy Use in Australia,
7 your own study from 2006, MDMA in Humans, your own study from
8 2006, MDMA in Humans?
9 A. The review paper.
10 Q. Yes. Your own 2009 study regarding cortisol?
11 A. Correct.
12 Q. The 2010 Kish study regarding brain imaging?
13 A. Right.
14 Q. I assume you submitted these studies because you found them
15 representative of what you consider a good indication of the
16 state of the scientific field today?
17 A. Originally I submitted about 24 studies but my counsel said
18 I had to reduce them.
19 Q. As did all the experts.
20 A. Which was a difficult choice. I was trying to give an
21 illustrative overview. I had to drop some very good articles
22 and include some qualitative articles just to give a flavor.
23 Q. But the six you picked you are pretty confident those give
24 a good overview?
25 A. They give an overview, yes.

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1 Q. A good one or just anyone?

2 A. Pretty good, yes.

3 Q. Three of the six articles were actually published in 2001
4 or earlier, is that correct?

5 A. If you say so. Yes.

6 Q. I listed Jansen 1999, Topp 1999, you 2001, you 2006, you
7 2009, and Kish 2010?

8 A. Right.

9 Q. We have half 2001 or earlier, half later?

10 A. Right.

11 Q. Do you think the pre 2001 studies still have a really
12 strong bearing on what we know about Ecstasy today?

13 A. Yes. All information to a scientist is useful, yes.

14 Q. In your 2001 paper, Human Pharmacology of Ecstasy, you
15 noted that there was a well-known reticence on the part of
16 journals to publish findings of no harm from Ecstasy; I am
17 paraphrasing. Is that correct?

18 A. That's what I wrote, yes, I believe it's still true.

19 Q. Given that, one might expect the literature to be skewed
20 towards findings of harm, to overrepresent papers in which harm
21 is found?

22 A. It depends on the size of the study. If it's a small
23 study, not finding significance, a journal is likely to throw
24 it out. If it's a large study with a large sample size, a
25 journal is likely to accept it even if it's nonsignificant, as

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1 in the most recent paper by John Halpern. It was a big sample
2 size; therefore, it's accepted. Had that study with
3 nonfindings been a small sample size, the journal would have
4 probably rejected it.

5 Q. With the small sample size studies with findings of harm,
6 the journal might well have accepted?

7 A. I think that's probably a bias, I guess; that would be my
8 guess, yes.

9 Q. How does that affect the conclusions you gave us earlier on
10 your direct that there is evidence going both ways on a lot of
11 questions? Does that concern you in light of the bias that
12 there is evidence going both ways but maybe there are some
13 things left out?

14 A. If I can answer that indirectly, Rodgers et al. looked at
15 sample size as a bias factor. They concluded that the sample
16 size was not affecting their conclusions.

17 Q. So you think the Rodgers meta-analysis did a pretty good
18 job of synthesizing this?

19 A. They are a bunch of statisticians so they should have done
20 a good job, yes.

21 Q. Getting back to some of the papers you submitted to the
22 court, the Jansen paper from 1999, that considered fairly
23 extraordinary cases. It was three case studies, right?

24 A. Yes.

25 Q. One of the case studies was an individual who indulged in

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1 binges lasting from Thursday to Monday, he was continuously
2 awake during that time, and he also used cocaine and marijuana?

3 A. Right.

4 Q. The second case study involved an individual who injected
5 MDMA 4 times a day and also used heroin and benzodiazepine
6 regularly?

7 A. Right.

8 Q. The third case study was an individual who had post
9 traumatic stress disorder and tended to take 25 to 30 tablets
10 of MDMA per weekend?

11 A. Right.

12 Q. 25 to 30 MDMA tablets per weekend, that's unusually large?

13 A. It's very large, yes.

14 Q. The Jansen paper was basically considering outliers?

15 A. I guess statisticians would call them outliers; I don't
16 believe the people themselves would call themselves outliers.

17 Q. The 1999 Topp study you put before the court involved a
18 group one-third of whom had been defined by the authors as
19 engaging in, quote, binging patterns, which the authors defined
20 as using on a continuous basis for 48 hours without sleep?

21 A. Right.

22 Q. Many of the sample were polydrug users?

23 A. Yes.

24 Q. In fact, within the past six months, 82 percent of the
25 sample had used amphetamines, 68 percent LSD, 40 percent

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1 cocaine, and 17 had used heroin?

2 A. Right.

3 Q. You wouldn't consider that a study that controlled well for
4 polydrug use.

5 A. It's an example of high-end users. I think I had 329
6 showing for a large number of people using MDMA in a pretty
7 chaotic pattern, yes. To throw your question back, if they are
8 outliers, it's a large number.

9 Q. The folks in the Topp study, many of whom binged, many of
10 whom regularly used other drugs, you are saying they are
11 outliers but there are a lot of them?

12 A. I am saying there are lots of Ecstasy users at the heavy
13 end of the scale. As you move up the Ecstasy usage pattern,
14 you tend to use more multiple drugs. So a lot of the heavy end
15 users move to a more chaotic pattern.

16 Q. I would think it would still be hard to separate out the
17 effects of MDMA itself when you have this, as you put it,
18 chaotic pattern of use going on with all those other drugs?

19 A. Sorry, rephrase that.

20 Q. Wouldn't be it be difficult to separate out the effects of
21 MDMA when there are so many other drugs going on and such heavy
22 use?

23 A. In the Topp study, it would. In fact, they didn't give
24 cognitive tests or anything. It's simply a just very
25 descriptive study of the problems reported by these users. The

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0C74MCC2 Parrott - cross

1 ecstasy users reported 8 physical problems on average and 4
2 psychological problems which they attributed to Ecstasy. These
3 are the heavy end of the Ecstasy usage scale and they chose
4 people using Ecstasy which they themselves state is associated
5 with a wide range of problems.

6 Q. Would you say that scientific studies are more probative
7 when the measures are conducted by scientists rather than
8 self-reported?

9 A. These were interviews with psychologists, so these were
10 interviews. The studies were funded by the Australian
11 government so the criteria were quite straight. My
12 recollection is that it was detailed interviews of users, I
13 seem to recall.

14 Q. That doesn't quite answer my question.

15 A. Structured interviews, that's my recollection of how I did
16 it.

17 Q. That doesn't quite answer my question. What I am looking
18 for is from a scientific perspective, wouldn't you put more
19 stock in a study where the scientists actually ran tests,
20 whether cognitive tests or brain imaging or other types of
21 scientific measures rather than simply asking people how they
22 felt?

23 A. If you are interested in neuroimaging you do a neuroimaging
24 study. If you are interested in cognition you do a cognitive
25 study. If you are interested in what problems people are

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0C74MCC2 Parrott - cross

1 reporting you give them structured interviews.

2 Q. All this study shows us is that people who use heavily and
3 use other drugs in the meantime report a lot of problems?

4 A. They report a lot of problems which they attributed to
5 Ecstasy.

6 Q. That wasn't scientifically verified; that was just their
7 own view of the matter?

8 A. It's what they said, yes.

9 Q. I would like to move on to some of your discussion of the
10 acute effects of MDMA, the immediate affects as you testified?

11 A. Right.

12 Q. You mentioned something called serotonin syndrome which you
13 described as meaning too much serotonin in the brain?

14 A. Yes.

15 Q. You said many users experience that?

16 A. Right.

17 Q. And you said it's usually mild?

18 A. Right.

19 Q. So when someone uses MDMA there is a temporary serotonin
20 spike then there is a return to normal?

21 A. There is probably a decrease in a few days afterwards, but
22 then back to normal after 7 days probably.

23 Q. Thank you for the correction; I will rephrase. When users
24 use Ecstasy, what you mean by serotonin syndrome is there is a
25 temporary uptick in serotonin then there is a decrease in

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0C74MCC2 Parrott - cross

1 serotonin, then about a week after use, it returns to normal?

2 A. Yes. So the syndrome refers to the acute period which is a
3 few hours after taking Ecstasy when you've got a boost in
4 serotonin. That's when people feel hot, often feel confused.
5 They display psychomotor aspects which hit the serotonin
6 syndrome checklist which was developed before Ecstasy was on
7 the scene.

8 Q. So, as a result of this serotonin syndrome, basically you
9 feel hot, you feel dizzy, you've got some motor coordination
10 problems?

11 A. That sort of thing, yes.

12 Q. Let's talk about cortisol. You mentioned that another of
13 the acute affects of MDMA is a sharp rise in cortisol?

14 A. Right.

15 Q. Cortisol is a chemical in the body that's associated with
16 stress?

17 A. Yes.

18 Q. There are other things besides MDMA that can lead to a rise
19 in cortisol?

20 A. Right, yes.

21 Q. Social stress might lead to cortisol?

22 A. All sorts of stress, yes.

23 Q. Let me rephrase that. Social stress might lead to a rise
24 in cortisol?

25 A. Yes.

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1 Q. Testifying in court might lead to a rise in cortisol?

2 A. Yes. I am glad you are not measuring my cortisol level
3 now.

4 Q. Mine too. An 800 percent increase in cortisol sounds like
5 a lot?

6 A. I think it is, yes.

7 Q. Exercise, would that increase your cortisol?

8 A. Yes. If you put somebody on a bicycle odometer which is
9 one of the bikes you see in New York where people are
10 exercising and pedal as fast as you can, physiologists call it
11 exercise to exhaustion, so instruct somebody to cycle as fast
12 as you can for 20 minutes, that's a standard physiological test
13 they use in physiology labs. The cortisol rise will be about
14 150 percent if you are not a very good cyclist. If you are a
15 fit cyclist, it will be about 80 percent. I cite that study in
16 one of my papers.

17 (Continued on next page)

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- 1 Q. How about a marathon runner after running a marathon, how
2 high would you imagine his cortisol?
3 A. I am not sure.
4 Q. Could it get as high as 800?
5 A. I am not sure. I have not seen the data.
6 Q. Is it possible that MDMA is not the only thing that
7 produces the rise in cortisol of the dimension that you
8 described?
9 A. I have talked to a couple of hormonal people at a
10 conference and they say it is a pretty extreme, because I
11 didn't know that much about cortisol before I started looking
12 into it so I started to check with some other people.
13 Q. I didn't know either.
14 But it goes away?
15 A. Sorry?
16 Q. The rise in cortisol goes away?
17 A. Yes. We measured for recovery in 24 hours after and it had
18 recovered.
19 Q. You used the term "chemical stressor" to refer to MDMA in
20 relation to its cortisol --
21 A. I think I am quoting Connors 2004.
22 Q. So MDMA like exercise, stress, testifying in court raises
23 your cortisol and then it goes back to normal?
24 A. Yes, it will do that.
25 Q. Now, I would like to make sure I understand one of the sort

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1 of general statements that you made last night at the beginning
2 of your testimony.

3 You testified that all of the deficits reported in
4 2001 have been confirmed by subsequent studies?

5 A. As far as I am aware, I think they have, yes.

6 Q. Let's talk about what that means. Does that mean that
7 there is some line in some study somewhere that suggested
8 perhaps the deficit was still there, or do you mean by that
9 something more robust?

10 A. Well, in science, you don't look at the individual trees,
11 you look at the forest and sort of get an impression. And I
12 think my impression is that those statements from 2001 have
13 been confirmed in general terms.

14 Q. You have also written that the effects of MDMA are
15 exacerbated by environmental factors?

16 A. That's right.

17 Q. So MDMA alone doesn't necessarily cause all of the problems
18 associated with MDMA? Are you sure you can really separate the
19 problems associated with MDMA from environmental factors and
20 other relatively common confounds like the use of other drugs?

21 A. For instance, if we are talking environmentally, in the
22 study I cited earlier, 2008 Parrott et al., Neuropsychobiology,
23 we had the Ecstasy users go to a rave and dance, and the only
24 drug allowed was alcohol, I think, possibly cannabis -- I have
25 to think about that, but definitely not to have any stimulants

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0C7UMCC3 Parrott - cross

1 and their cortisol levels were not significantly altered by
2 partying.

3 Q. It is interesting though, in your 2006 paper, Dancing Hot
4 on Ecstasy --

5 A. Right.

6 Q. -- I apologize. I am sure I am leaving out the longer
7 subtitle, you list as important factors in some of the MDMA
8 associated problems you found, lifetime use of Ecstasy, hot and
9 crowded conditions and the use of other drugs?

10 A. Right.

11 Q. So there are really lots of contributing factors to the
12 problems you described as coming from Ecstasy, according to
13 your own work?

14 A. There are lots of drug factors that interact with Ecstasy,
15 for instance, alcohol increases the pleasure rating of Ecstasy.
16 So there are reasons why people co-use drugs.

17 Q. You also wrote in 2006 in a study called "Problematic
18 Versus Non-Problematic MDMA Ecstasy Use" -- bear with me.

19 A. Sorry. 2000 and -- is that 2001?

20 Q. Bear with me.

21 2006 article that you co-authored called "Problematic
22 Versus Non-Problematic" --

23 A. Was that Soar, et al.?

24 Q. Let me check.

25 Yes.

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1 A. That was written by one of my research students.

2 Q. S-O-A-R.

3 A. That's right.

4 Q. And the other authors are Turner and you?

5 A. Right.

6 Q. So you are familiar with that paper?

7 A. I haven't read it in a while, but I was a co-author, yes.

8 Q. I would like to quote from it, and I hope you will bear
9 with me.

10 On page 421, you say: "The current study supports the
11 idea that problematic Ecstasy use may be due to premorbid
12 vulnerability in individuals, i.e., in those individuals that
13 report problems associated with their Ecstasy use. The data
14 indicated that a greater number of problematic Ecstasy users
15 reported previous psychiatric history and were more likely to
16 have a family history of psychiatric illness compared to
17 non-problematic Ecstasy users, thus premorbid psychiatric
18 differences may have contributed to these Ecstasy related
19 problems."

20 A. That's what we found in that study, yes.

21 Q. When you say premorbid, what you do you mean?

22 A. Before taking the Ecstasy.

23 Q. So preexisting?

24 A. Preexisting, yeah.

25 Q. So basically you are saying that a number of the problems

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0C7UMCC3 Parrott - cross

1 associated with Ecstasy may well be due to problems that
2 existed in the subjects before they took the Ecstasy?

3 A. In that study we found that, yes. What we found was that
4 they had problems after Ecstasy, but they also had problems
5 before. The crucial question is, what has happened to their
6 problems.

7 Q. Then in the 2006 "MDMA in Humans" review that was submitted
8 to the Court for this hearing, you pointed out that it was
9 difficult to separate the consequences of marijuana use from
10 the consequences of MDMA use because 90 percent of MDMA users
11 also used marijuana?

12 A. It is difficult, yes, and there is high co-usage, yes.

13 Q. You also wrote just this year in an article entitled
14 "Procedural and Declarative Memory" -- and again I apologize if
15 that's not the full title --

16 A. That is Blagrove et al.?

17 Q. That's correct.

18 You write on page 10: "This association of recent
19 Ecstasy MDMA use with poor declarative recall was only
20 significant for participants who also reported having used
21 other illicit drugs 24 to 48 hours prior to testing."

22 A. Yes. We found that, yes.

23 Q. So it sounds to me like, as a whole, a lot of the research,
24 including the recent research finding problems with Ecstasy has
25 been confounded by polydrug use and preexisting conditions?

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1 A. Yes. That's what I reviewed from 2006 when I concluded
2 there my review that cannabis was an important co-drug, that it
3 had very complex modulator effects on MDMA. Cannabis could
4 have had adverse effects. MDMA could have had adverse effects,
5 and they often occur together. So cannabis and MDMA interact
6 together in very complex ways, yes.

7 In the Blagrove paper we also found MDMA related
8 deficits which were not explained by the cannabis. But some
9 were -- it is complicated.

10 Q. Sure.

11 Now, one of the papers you placed heavy reliance on in
12 your testimony today is the Kish 2010 brain imaging --

13 A. Right.

14 Q. We heard all of the experts who testified rely on Kish, so
15 he is a pretty respected researcher?

16 A. The study we cited was evidence, yes, we focused on that
17 study.

18 Q. Sure.

19 A. What is interesting is that Kish in 2002 he published a
20 review where he was very quiet skeptical, he raised a question
21 as to whether it was MDMA, so it is quite interesting that he
22 has now published this paper showing quite very solid evidence
23 for deficits.

24 Q. So in the Kish paper -- I would like to read you a quote
25 and ask you if you agree with his conclusion and

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0C7UMCC3 Parrott - cross

1 characterization. He writes that most Ecstasy users reported
2 "the typical acute effects of Ecstasy, including increased
3 sociability and hyperthermia and features of a drug
4 discontinuation withdrawal system sometimes severe, occurring
5 one or more days after cessation of drug use and that resolved
6 within a week"?

7 A. Yeah.

8 Q. So that is a fairly typical acute experience of an Ecstasy
9 user, you would agree?

10 A. Yes. It seems to be described in fairly standard ways,
11 yes.

12 Q. So the typical Ecstasy user has increased sociability, gets
13 hotter, a few days later has a temporary withdrawal feeling but
14 then returns to normal?

15 A. Yes. That would be good summarization, yes.

16 Q. Pardon me for one moment while I find my place in my notes.

17 You have testified today that MDMA is neurotoxic?

18 A. Yeah. According to the neuroscience papers I have read it
19 is, yes.

20 Q. That's the case over the long-term or just temporarily?

21 A. As I say, that is still to be resolved. That issue, it is
22 not clear how long -- we need to replicate the Kish study with
23 people who have been drug free for a while to see.

24 Q. But --

25 A. In functional terms, as I mentioned earlier, there is a

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0C7UMCC3 Parrott - cross

1 Morgan study, a Zakzanis study. It is a wide open question,
2 but there are indicators that they are enduring over time.

3 Q. You wrote a paper in 2007 entitled "Ecstasy versus
4 Alcohol"?

5 A. Right.

6 Q. And referring to serotonergic neurotoxicity, you said that
7 there is evidence for structural recovery following drug
8 cessation?

9 A. Yes. That relates to the Reneman paper where they found --
10 I think they reviewed six studies or five studies. And I think
11 in four of the five, there was a correlation between duration
12 of abstinence and degree of serotonin loss.

13 So in all of those studies, they showed serotonin loss
14 but it was less in those who had been abstinent for the longest
15 period. That is my understanding of the Reneman review.

16 So that, again, it doesn't show recovery because all
17 of those studies showed deficits. So all of the studies showed
18 serotonin marker deficits. But the degree of deficit seemed to
19 be associated so --

20 Q. I just heard you say that it didn't show recovery, but in
21 your paper you wrote: "There is evidence for structural
22 recovery following drug cessation."

23 A. Yes. So in the Reneman paper, there is this correlation,
24 so that the longer you have been off it, the less damage you
25 still have in your system.

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0C7UMCC3

Parrott - cross

1 So the suggestion from Reneman, which I believe I was
2 probably using for that statement, was that there may well be
3 some recovery. But, crucially, in those studies, even those
4 which are showing recovery, there was still impairment.

5 So there is indication from that literature that there
6 may well be recovery, although people are still impaired.
7 Basically, it is a wide open question.

8 We can't give particularly good evidence on that. It
9 is all suggestive.

10 Q. It sounds to me like we are really narrowing down the
11 spectrum of harms here. It used to be, we thought there was a
12 great deal of neurotoxicity and now we recognize there is
13 recovery and maybe just a small deficit remains?

14 A. Well, the animal literature has always been clear that if
15 you stop getting MDMA, you will get what Val Curran described
16 as pruning. So you get resurgence of axon and dendrites near
17 to the Raphe nuclei cell. But as Val Curran noted, you don't
18 get the full axon regeneration.

19 So the animal literature suggests there should be some
20 degree of recovery, although it would suggest you won't get
21 full recovery.

22 Q. So you agree then, just yes or no, that contrary to what
23 was believed in 2001, we now know there is a good deal of
24 recovery with respect to the axons?

25 A. We certainly don't know that, no.

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0C7UMCC3 Parrott - cross

1 Q. I'm sorry? Didn't you just say that?

2 A. You said a good deal of recovery? I said that the evidence
3 was that there was an association between time of abstinence
4 and degree of impairment, but even in that, the users were
5 still impaired. So it is an association of relative. It is
6 not a good deal of recovery.

7 Q. So there --

8 A. Most were still impaired.

9 Q. We now know that there is some degree of recovery?

10 A. From the Reneman conclusions, that would suggest some
11 degree of recovery. Many people believe that biological
12 systems should show some degree of recovery.

13 Q. Contrary to what was believed in 2001?

14 A. No. The animal literature prior to 2001 suggested that
15 when animals stopped being given MDMA, you get a degree of
16 recovery, but not permanent. That was known prior.

17 Q. So is it your testimony then that the scientific
18 understanding of MDMA changes on the brain is essentially the
19 same as it was in 2001 or worse?

20 A. It is very -- it is similar, but more sophisticated. So in
21 2001, the hypothesis was that MDMA would be causing serotonin
22 damage in humans, and there were a couple of studies indicated
23 that.

24 Since 2001, there's been a number of studies reviewed
25 by Cowan, reviewed by Reneman. And Cowan said that the most

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0C7UMCC3 Parrott - cross

1 consistent finding is a reduction of serotonin transporter
2 density. So Cowan's review is that there are a number of
3 studies confirming serotonin loss in the higher brain regions.
4 Kish is consistent with that. It is slightly better in a few
5 ways, but it is very consistent with findings over the last 10
6 years.

7 Q. Let's hang on for a second, though. You said it was
8 slightly better, so you would agree that the degree of
9 serotonin transporter loss has been shown to be less than it
10 was thought in 2001?

11 A. No. No.

12 Q. That's curious because --

13 A. The Kish study shows reductions of 20 to 40 percent in
14 different cortical brain regions, 50 percent loss in the
15 insular which is an important brain region.

16 Q. Let me quote to you from Kish: "We did not find a global
17 massive reduction of brain SERT finding as reported in the
18 first SERT imaging study of Ecstasy users," citing McCann,
19 1998.

20 A. He then discusses the reasons for that. And he also
21 discusses why he didn't replicate Buchert et al. in 2002 or
22 2004 where Buchert found reductions in an area called the
23 limbic, the striatum.

24 Q. That's all well and good, but what I heard him to be saying
25 was -- and if you could tell me yes or no, am I correct -- am I

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1 correct that Kish found less SERT finding deficits than had
2 been understood in 2001, yes or no?

3 A. I would have to check the McCann paper. I would have to
4 check that.

5 Q. Do you disagree with this statement from Kish: We did not
6 find a global, massive reduction of brain SERT findings as
7 reported in the first SERT imaging study of Ecstasy users by
8 McCann?

9 A. Yes. I agree with that statement.

10 Q. So then it follows, does it not, that more recent brain
11 imaging has shown less SERT depletion than was understood to be
12 the case in 2001?

13 A. No. Because Buchert found reductions in the striatum.

14 Q. But Kish didn't?

15 A. Well, to answer your question. Buchert, after 2001, found
16 reductions in the striatum. Kish discusses that study and
17 says, for reasons, it is probably because Buchert had heavy
18 users.

19 Kish then hypothesizes that their moderate users, it
20 was affecting the highest brain regions. They were not
21 affecting the limbic system because Buchert had higher users
22 and McCann had the highest users.

23 So the two studies showing the most intense of Ecstasy
24 users, showed regions, not only the brain cortex, but also the
25 limbic system. And that's what McCann reported in '98.

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1 Q. So now what I hear you saying is that Kish's work isn't of
2 that much value because he didn't replicate McCann or the other
3 fellow Buchert.

4 MR. KOBRE: Objection.

5 THE COURT: Sustained as to form.

6 Q. Are you saying that the Kish study is problematic because
7 it failed to replicate the deficits found earlier?

8 A. No, not at all. It is not problematic. They discuss why
9 they didn't find reductions in the striatum, which they
10 predicted. And they say it may well be because their users
11 were less heavy users than those in Buchert and those in
12 McCann -- the Buchert post 2001 and the McCann pre 2001. So
13 2001 is an artificial distinction.

14 Q. Sure. But what I am getting at, is Kish found less damage
15 than previous studies, yes or no?

16 A. No. Some previous studies found less.

17 Q. Kish found less damage than some previous studies?

18 A. Than Buchert and McCann, yes.

19 Q. In 2001, was McCann the major brain imaging study that had
20 been published on MDMA?

21 A. I think there was the study -- was it when was that
22 published. I am not sure. Sempel was one of the earlier
23 studies, and the McCann --

24 Q. McCann was pretty well known?

25 A. McCann was, I believe, the first of the neuroimaging

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1 studies. I may be incorrect on that, but that's my belief.

2 Q. Kish also notes, quoting from Kish -- referring to another
3 recent study he says it "suggests that any drug-induced SERT
4 reduction might be reversible." So again evidence for not
5 long-term damage?

6 A. Yes. Most biologists believe that when you get rid of it,
7 you will have biological recovery to an extent. It is a
8 general biological principle.

9 Q. So let's talk about neurocognitive functioning. You talked
10 a lot about that on your direct?

11 A. Right.

12 Q. In neurocognitive functioning, would it be fair to
13 categorize all of the following areas as subfields of
14 neurocognitive functioning: Executive function and logic,
15 prospective memory, verbal memory and working memory?

16 A. Right.

17 Q. You have described in detail for us today a handful of
18 studies finding problems?

19 A. Right.

20 Q. But as you yourself noted, in some of the studies you
21 yourself cited, there were problems with the controls.

22 I am sorry. Let me start that question over.

23 But as you yourself noted, in some of the studies you
24 yourself cited, they failed to control for important variables?

25 A. There is always issues over control, yes.

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1 Q. In fact, you said that the prospective memory study by
2 Rendell failed to insure that the Ecstasy users tested had been
3 drug free through what you have termed the washout period of
4 about a week?

5 A. No. The Rendell study only asked people to be drug free, I
6 think, it was for one day or two days -- which is a very naive
7 request. Most drug studies specify the drugs, don't drink
8 alcohol for a day, don't smoke cannabis for two days, don't
9 take stimulant drugs for a week.

10 Q. So Rendell failed to insure that participants were drug
11 free --

12 A. In their instructions, as I say, they are very light users,
13 either less than once a month in one group, more than twice
14 every month in the other group. So it is unlikely that they
15 tested someone in that washout period, although it is a
16 possible issue with that.

17 Q. So we sort of have to make a leap here that they had
18 been -- that the subjects went through the washout period?

19 A. I cannot imagine a research assistant bringing someone into
20 the lab who has just taken the drug.

21 Q. One of your examples of an executive function and logical
22 reasoning study, the Fisk study, you noted that there was a
23 failure to control for polydrug users?

24 A. Not a failure to control for. When they looked for
25 polydrug, they found, I think, it was use of cocaine and

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0C7UMCC3 Parrott - cross

1 amphetamine were also influential in being associated with the
2 logical reasoning impairments, yes.

3 Q. Did you say that these neurocognitive impairments were
4 long-term or acute?

5 A. In the Fisk study, they were all current users, but they
6 were drug free when tested.

7 Q. In general, is it your testimony that the neurocognitive
8 impairment is a long-term consequence?

9 A. Yes.

10 Q. But as you noted in your testimony, there are some reports
11 of unimpaired performance?

12 A. Right.

13 Q. Including some of your own studies, in fact, in a 2002
14 paper called --

15 A. Is that --

16 Q. "Neuropsychological Evidence" by Fox?

17 A. Fox, et al., 2002, Psychopharmacology.

18 Q. That's right. You noted that "Ecstasy users remained
19 unimpaired on most measure of pre-frontal function," is that
20 right?

21 A. Yes. That was an unusual study. And Helen Fox found
22 deficits in the temporal lobe. What she did is a very
23 interesting study. She did the CANTAB, the Cambridge Automated
24 Neuropsychological Test Battery, which is a standard battery of
25 cognitive tests. And she linked up with Barbara Sahakian from

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0C7UMCC3 Parrott - cross

1 Cambridge University who had profiles for cognitive test
2 profiles for various people with various forms of brain
3 damage --

4 Q. I'm sorry, Doctor. Just for reasons of time, could we just
5 get a yes or no: Ecstasy users remains unimpaired on most
6 measures of prefrontal functioning, yes or no?

7 A. Yes.

8 Q. And more recently, you suggested in your 2006 paper, "MDMA
9 or Ecstasy: The Contemporary Human -- I don't have the full
10 title -- "and Animal Perspective," you stated, "On many
11 assessment measures, performance levels remained unimpaired
12 even in heavy users." Yes or no?

13 A. Yes.

14 Q. And in your 2006 review, "MDMA in Humans," which you have
15 submitted to the Court on page 148, you state: "The literature
16 provides extensive evidence of unimpaired neuropsychological
17 biological functioning," yes or no?

18 A. Yes.

19 Q. In your 2010 paper on procedural and declarative memory,
20 you stated: "The procedural memory performance of recent and
21 abstinence, Ecstasy and MDMA users did not differ from
22 controls." Yes or no?

23 A. Yes.

24 Q. So you have also said in your testimony that there is
25 evidence going both ways on a lot of things?

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0C7UMCC3

Parrott - cross

1 A. Yes.

2 Q. Including it sounds like neurocognitive functioning?

3 A. Yes.

4 Q. So isn't it best then in evaluating this large body of
5 literature with some times disparate results, to use a
6 meta-analysis like Rogers?

7 A. Exactly, yes.

8 Q. Now, Rogers concludes -- and this is from the executive
9 summary -- "The evidence we identified for this review provides
10 a fairly consistent picture of deficits in neurocognitive
11 functioning for Ecstasy users compared to Ecstasy naive
12 controls.

13 Although the effects are consistent and strong for
14 some measures, particularly verbal and working memory, the
15 effect sizes generally appear to be small when single outcome
16 measures were pooled, the mean scores of all participants
17 tended to fall within normal ranges, yes?

18 A. Right.

19 Q. And on direct -- I believe this was last night -- you
20 testified that Kish found memory impairments?

21 A. Right.

22 Q. But again quoting from Kish: "Nevertheless, most Ecstasy
23 users had few cognitive complaints after the acute effect and
24 the drug withdrawal phase had passed and user values generally
25 fell within the normal control range, is that correct?

SOUTHERN DISTRICT REPORTERS, P.C.

(212) 805-0300

0C7UMCC3 Parrott - cross

1 A. If you are reading out, yes.

2 Q. He goes on to state, again from page 1793, both of these
3 last two quotes: "The observation of normal or close to normal
4 performance on cognitive testing is consistent with much of the
5 Ecstasy literature." Yes?

6 A. Yes.

7 Q. So it sounds to me like Rogers, who we have all agreed has
8 done a full review of the literature encompassing thousands of
9 studies and Kish seem to agree that -- and Kish, we have all
10 noted is respected, and all of the experts we have relied on,
11 everyone seems to agree overall, there are pretty slight
12 neurocognitive effects, would you say that?

13 A. I think they agree that consistently significant effects,
14 significant overall.

15 Q. When you say significant, you mean statistically
16 significant?

17 A. Yes.

18 Q. But slight in terms of amount?

19 A. Within the normal range in that people can still function
20 within broadly normal limits, although they are impaired.

21 Q. You seemed to testify otherwise, based on your own review
22 of the literature in 2006. Do you think there's a discrepancy
23 between your 2006 work and the Rogers and Kish conclusions we
24 have just discussed?

25 A. Well, what Rogers did is took all of the studies together

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(212) 805-0300

0C7UMCC3 Parrott - cross

1 and averaged them. So one of the strange things I found was
2 that the dosage -- they were simply throwing all of the data
3 into a great big pool and saying what is the mean score.

4 So in average terms, you have this slightly impaired
5 average user. What I was doing and what most reviewers do --
6 the Rogers review is atheoretical. They have no theory. That
7 is statisticians -- they are simply taking averages from
8 everything.

9 What I was doing in my 2006 review is saying, we have
10 this variation in findings. Why have we got this variation in
11 findings? So I was taking a theoretical approach to try to
12 explain the variance, which Rogers didn't attempt to do.

13 Q. What do you mean by theoretical approach? You had a theory
14 and you were trying to confirm it?

15 A. As I said earlier, I was looking at what are the factors
16 explaining the differences between studies. Why did Croft et
17 al. in 2001 find two very different studies findings between
18 their two studies.

19 And I said it may well be because one study had very
20 heavy cannabis users and the other study had very heavy Ecstasy
21 users. And that may well explain why one study found Ecstasy
22 related deficits, the other study found cannabis related
23 deficits.

24 So in terms of the average user, people that use very
25 little to people that use a lot, the average effect over

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(212) 805-0300

0C7UMCC3 Parrott - cross

1 everyone will be significant but not particularly marked. On a
2 heavier user, the literature suggests, with lifetime cumulative
3 Ecstasy use, you are more impaired. So the literature suggests
4 the effect is stronger in those that use the drug more in their
5 lifetime.

6 Q. So once again we are back to the point that, as with most
7 drugs, if you take a lot of them they can be damaging when a
8 small to moderate dose would not?

9 A. As with Kish, those with more serotonin loss showed worse
10 memory.

11 Q. So yes or no, you agree that it is simply the case that
12 higher use correlates with more harm?

13 A. Yes.

14 Q. And that is typical of most drugs?

15 A. Of many drugs, yes.

16 MR. MICHAELMAN: Thank you very much.

17 THE COURT: Redirect examination.

18 MR. KOBRE: Yes, your Honor. Thank you.

19 REDIRECT EXAMINATION

20 BY MR. KOBRE:

21 Q. Professor Parrott, on cross-examination counsel asked you
22 about addiction and dependence on MDMA. Now, are there ways in
23 which MDMA causes dependence?

24 A. In heavier users, they report difficulties going without
25 the drugs. Some of them say they want to quit using the drug

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(212) 805-0300

0C7UMCC3 Parrott - redirect

1 but still use it. Some users report spending too much time
2 thinking about the drugs or planning to use it. And these were
3 reports from the Bruno study in 2008.

4 Q. Are there users of MDMA that are heavy users?

5 A. Yes.

6 Q. What do you consider to be a heavy user?

7 A. Well, the Bruno study has a table on this. Describing the
8 group who had problems. I can't recall the details of the
9 table, but they were heavier users compared with the group who
10 didn't show this dependence syndrome. So some of them were
11 using Ecstasy more than once a week.

12 Q. Did the Bruno group administer MDMA like in a laboratory
13 environment or were they taking people who had actually used
14 MDMA prior?

15 A. It was a survey of 1,500 people who were drug free when
16 interviewed.

17 Q. So some of those 1,500 were heavier users?

18 A. Yes. I can't recall from their table. The only one that I
19 can recall was, I think 60, 70 percent reported using Ecstasy
20 more than once a week, at least once in the past six months and
21 their lifetime usage, I recall, was heavier than those, but I
22 cannot recall the figure.

23 Q. Can you give a sense of what percentage of users would be
24 heavier users versus lighter users?

25 A. What percentage?

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(212) 805-0300

0C7UMCC3

Parrott - redirect

1 Q. Or just give a general sense of how frequently or
2 infrequently we would find a heavier user?

3 A. Well, all of the studies define heavier user in different
4 ways. It is a very sensible question, but I am afraid I cannot
5 give an estimate.

6 Q. You mentioned earlier the Morgan study. Does the Morgan
7 study have a definition of heavier or less heavy user?

8 A. Morgan simply looked -- Morgan strictly looked at former
9 users v. current. I cannot remember what usage data he had in
10 that study.

11 Q. You testified on cross-examination about the cognitive
12 studies. Now, the study that you referred to on direct, the
13 cognitive studies showing cognitive deficits, were those
14 deficits only showed in heavy users?

15 A. I'm sorry. Which studies?

16 Q. You talked about a number of cognitive deficits about
17 memory and what counsel referred to. He sort of lumped them
18 all together, the memory and executive function?

19 A. Right.

20 Q. Were those deficits only found in heavy users? Are those
21 studies all specifically with regard to heavy users?

22 A. No. You often find dose related effects. So in the Fox et
23 al., 2001, that is the paper where we got the prize from the
24 British Association for Psychopharmacology. We found that
25 there was an increase in level of problems that you stepped up

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0C7UMCC3

Parrott - redirect

1 the dosage scale. So the light users were marginally worse
2 than the non-users. Then the moderate users were better off
3 than the heavier uses who were further impaired.

4 Q. It sounds like many of these studies actually involved some
5 heavy users?

6 A. Many studies have done, yes.

7 Q. And these were all studies where the subjects were drawn
8 from the general population of Ecstasy users, is that right?

9 A. Yes.

10 Q. So would it be fair to say that there are enough heavy
11 users to go around to provide --

12 A. I see what -- yes. In the Fox study, we took a three-way
13 split to allocate the groupings into three fairly equal sized
14 groups -- that's my recollection anyway.

15 Q. What I am getting at. You testified that in all of these
16 studies or many of these studies, were groups of heavy users?

17 A. Yes. In the Fox et al. study about a third of the users --
18 that was my recollection -- and that was the finding using over
19 100 times lifetime.

20 Q. So is heavy use of Ecstasy rare?

21 A. No.

22 Q. Heavy use of Ecstasy is not rare?

23 A. No.

24 Q. Now, Professor Parrott, is it particularly important in
25 trying to get at the practical effects of MDMA, is it

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0C7UMCC3

Parrott - redirect

1 particularly important to control for what you refer to as
2 premorbid psychiatric issues?

3 A. If you are looking at psychiatric problems, yes. You want
4 to know, do they exist before or not, as part of your
5 investigatory procedures.

6 Q. My question is, if we are trying to assess the harm of
7 MDMA, is it important to look at both people with prior
8 psychiatric problems and people who did not have prior
9 psychiatric problems?

10 A. Yes. You have different types of study. As I mentioned
11 before, the McCann study looked at people without prior
12 diagnoses, and they found that taking Ecstasy led to -- it was
13 associated with depression. And they said it was associated
14 with binge use, so using Ecstasy for more than 12 hours was
15 associated with later depression. And they screened out
16 anybody with a prior psychiatric problem in that study. Also,
17 it is very crucial because MDMA is used by people with
18 psychiatric problems. It is crucial to know what effects, you
19 know, to test that population.

20 Q. Why is that important?

21 A. Well, because some Ecstasy users have prior problems so we
22 want to know, you know.

23 Q. What?

24 A. We want to know what is happening to those people. Is it
25 worsening problems? Are the problems not getting worse? Are

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0C7UMCC3 Parrott - redirect

1 they getting better. That is why it is important.

2 Q. Are there some studies showing that Ecstasy can actually
3 worsen prior psychiatric issues?

4 A. I can't recall any that has looked at that. There are
5 studies in psychiatric hospitals where they have looked at use
6 of drugs and problematic drugs in the U.K.

7 It is a big problem, the usage of all recreational
8 drugs by people with prior psychiatric problems. But it is
9 actually very difficult to conduct such studies because of
10 clinical, ethical reasons.

11 Q. What you are saying, the question about whether Ecstasy use
12 can worsen or somehow interact with prior psychiatric problems,
13 that question has not yet been answered in scientific
14 literature?

15 A. It would be nice to be able to look at that. I cannot off
16 the top of my head recall such a study. They may well exist,
17 but at the moment I can't recall any.

18 Q. Would it be a problem if Ecstasy use worsens prior
19 psychiatric problems?

20 A. If that was found, it would be a problem, yes.

21 Q. Now, counsel on cross asked you about some of the articles
22 that were submitted to the Court, some of the six articles.
23 What were your criteria for choosing those articles?

24 A. Well, I have been criticized for choosing the Jansen
25 article, and I couldn't decide whether to include the Bruno

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0C7UMCC3

Parrott - redirect

1 article which is in Australia on the sample of 1500 versus the
2 case study. But I included the case study because it
3 illustrates the sort of intensive usage you do find in some
4 people at the extreme end of the spectrum. So it shows that
5 MDMA is problematic for people at the heavy end who are using
6 it in a very problematic way.

7 Q. And these people at the heavy end, putting aside Jansen,
8 sort of just heavier use, what's been talked about heavier use
9 in the papers, how commonly does that occur?

10 A. It is quite rare because most people quit using the drug
11 before that stage.

12 What you tend to find is people have a honeymoon
13 period when they start taking the drug, where it is very few
14 problems. And then they go through a stage of intensifying
15 their use, they have a chronic tolerance.

16 Then they either decide to quit because it is causing
17 more problems than gains, or they carry on using, in which case
18 they need to move up to the heavy end of the usage spectrum,
19 and then they will often use it with multiple other drugs.

20 Q. During the period of intensifying use, would those people
21 be considered heavy users?

22 A. Yes.

23 Q. Does that happen pretty commonly?

24 A. As I say, it is one of those drugs which is very strange in
25 that people tend to take it less frequently over time. This

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(212) 805-0300

0C7UMCC3

Parrott - redirect

1 has been found in a couple of studies, which is very unusual
2 for drugs.

3 So what seems to be happening, they are developing
4 more problems. They are developing more problems. They then
5 develop these desires to have the drug, but they are having
6 problems with the drug. So have this balancing effect of
7 cost-benefit ratio so they are taking it less frequently, but
8 still go back to using.

9 It is very strange for a drug to be used less
10 intensively over time. Most users then quit although some
11 people will continue intensifying their usage.

12 We tested one such person, and that was published in
13 Soar et al. My research assistant tested someone who used very
14 heavy Ecstasy for three years. It was massive problems. They
15 have been abstinent for seven years, and they still have these
16 problems. They had wide-ranging problems. In the intervening
17 years they were heavy users of multiple drugs. So it is a very
18 chaotic pattern.

19 Q. You mentioned on cross-examination that lots of Ecstasy
20 users are at the heavy end of the scale?

21 A. I'm sorry?

22 MR. MICHAELMAN: Objection. Mischaracterizes his
23 previous testimony.

24 THE COURT: Why don't you just put a question to the
25 witness.

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0C7UMCC3

Parrott - redirect

1 BY MR. KOBRE:

2 Q. In your study about cortisol that we discussed on direct,
3 you were asked on cross about whether that cortisol effect goes
4 away, it is only there in acute stage. What are the long-term
5 effects, though? Are there long-term effects of the acute
6 cortisol increases?

7 A. There is a study by Gerra et al. -- I think it is 2002 --
8 which looked at cortisol levels in drug free, abstinent Ecstasy
9 users, and I think they found a deficit in users. But I think
10 they also replicated the study on other occasions and didn't
11 find a deficit. So it is unclear about the long-term effects
12 on cortisol.

13 Q. I think you were asked on cross-examination whether these
14 increases in cortisol are just like exercise. Are the
15 increases in cortisol that you found in your study as a result
16 of MDMA use, are they similar to the ones that are typically
17 found in exercise?

18 A. No. They are far stronger. And one of the problems of
19 MDMA is that it tends to stimulate release of all
20 neurohormones. You get a release of testosterone. You get a
21 release of progesterone, prolactin -- a whole range of hormones
22 are increased by acute MDMA.

23 Q. Counsel asked on cross-examination about your testimony
24 that sort of the harms that were associated with MDMA before
25 2001 having been confirmed. Were there studies subsequent to

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(212) 805-0300

0C7UMCC3 Parrott - redirect

1 2001 confirming, for example, the cognitive deficits that you
2 testified to?

3 A. Yes. Many studies since 2001 have found cognitive
4 deficits.

5 Q. And those are studies specifically to determine whether
6 MDMA use -- were those studies specifically to determine
7 whether MDMA use impairs cognitive ability?

8 A. Yes. There have been lots of studies saying there is an
9 association between Ecstasy use and cognitive deficits, yes.

10 Q. Professor Parrott, you were also asked about the effect of
11 environmental factors?

12 A. Right.

13 Q. Is it important -- are the effects of environmental factors
14 important when looking into the harms of MDMA?

15 A. Yes. There's an animal study. I cannot remember the
16 authors now, but they found when laboratory rats were given
17 MDMA, it is more re-enforcing in the heat, in other words, the
18 rats button press more for the drug.

19 Q. Turning to the humans, if we are interested in determining
20 how harmful MDMA is to humans, is it important to look at
21 humans in the typical environment in which MDMA is used?

22 A. I believe it is, which is why we do those studies.

23 Q. Why is that?

24 A. If MDMA is more enforcing in the heat, the theory is that
25 Ecstasy users may find more pleasure when they become hotter.

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0C7UMCC3

Parrott - redirect

1 So it is not just the drug itself, it is the drug plus the
2 heat. So it may well be the reason for the association between
3 MDMA and raves is that raves provide the ideal environmental
4 conditions to boost the effects of the drug.

5 Obviously if you are boosting the effects of the drug,
6 that may well have an acute increase, but it may well lead to
7 problems later. And that is what we have found in a study we
8 published in 2006 in the journal Human Psychopharmacology
9 called Dancing Hot on Ecstasy.

10 Q. So actually in assessing the harms of MDMA, is it actually
11 more important to assess them in the environment this which
12 MDMA is typically used?

13 A. I think it is probably more damaging in the hot
14 environments of raves than it is in the laboratory. What we
15 found there was that people who danced continuously or felt hot
16 reported more problems the days afterwards.

17 Q. You were asked about the Soar et al. study?

18 A. Right.

19 Q. And could you describe what the methodology and the
20 conclusions of that study were briefly?

21 A. I hadn't read that study for many years, so I am afraid I
22 can't answer that.

23 Q. Professor Parrott, I think you spoke with counsel about the
24 question of whether there is recovery to the serotonin neurons.
25 Can you explain whether there is recovery and whether recovery

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(212) 805-0300

0C7UMCC3

Parrott - redirect

1 proceeds to baseline, whether there is full recovery, how that
2 occurs?

3 A. It is my understanding, based on the Reneman review of
4 2006, people were still impaired.

5 Q. Is that in each of the studies that Reneman looked at?

6 A. My recollection of Reneman review was that they found
7 consistent finding for damage.

8 Q. Does that imply anything to you with regard to whether
9 there is recovery at the baseline?

10 A. As I say, the studies have yet to be performed to follow up
11 users over many times, but certainly the studies covered in
12 various views which are on current users or people who have not
13 used for a fairly moderate period of time rather than long
14 period of time, show that the deficits are there.

15 Q. You mean that the deficits remain?

16 A. The deficits are there for the limited period of time that
17 people have studied.

18 Q. Could you tell us how, with respect to the deficits in
19 serotonin transporter and the axon damage, has there been any
20 kind of significant change in the scientific consensus of
21 scientific opinion prior to 2001 versus after 2001 and up to
22 the present?

23 A. Well, prior to 2001, the evidence is very limited, but
24 since then, the broad general findings have been confirmed.

25 Q. And those findings are?

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0C7UMCC3

Parrott - redirect

1 A. That reduced serotonin in the cerebral hemispheres in many
2 studies and some studies also show deficits in the subcortical
3 deficits of the limbic system, but not all studies show that.

4 Q. I think that you were asked about Kish and your conclusion
5 that Kish didn't find a global decrease in SERT. What does
6 that mean?

7 A. Well, in Kish's discussion he said, we predict to find
8 deficits in the striatum, which is a part of the limbic system.
9 They didn't find that, and they were surprised by that because
10 Buchert had found that and McCann had found that.

11 So they then looked at the McCann and Buchert papers,
12 and they hypothesized that it may well be because Buchert and
13 McCann had used heavier users and that there are a couple of
14 sentences in the Kish report which says that there were some
15 indications in the Kish study that their heavy users may well
16 have had the start of a deficit in the striatum, but they
17 didn't present any data, it was just a sentence in the
18 discussion.

19 Q. Did Kish find that other parts of the brain were affected?

20 A. Kish found that all areas of the cerebral cortex were
21 affected and the hippocampus. So those were the two brain
22 areas but, obviously, the cerebral cortex is the vast majority
23 of the brain.

24 Q. What Kish found was there were some parts of the brain that
25 were not affected but other parts were certainly affected?

SOUTHERN DISTRICT REPORTERS, P.C.

(212) 805-0300

0C7UMCC3

Parrott - redirect

1 A. Yes. So the traditional areas for deficits were confirmed
2 in the Kish study. And one finding they found was that the
3 insular which is a very small part of the brain in the region
4 between the frontal cortex and the temporal lobes. It is a
5 tiny area. The reduction there was 51 percent, which is a very
6 big reduction.

7 And they say that is important for awareness, which I
8 was intrigued by because in the Helen Fox study published in
9 2001, we found that Ecstasy users had memory problems and
10 reported that they didn't have problems related to Ecstasy. So
11 when I saw that, I was quite intrigued as to whether that might
12 explain some of the Fox findings.

13 Q. Counsel also asked you about some of the neurocognitive
14 studies and whether they controlled for confounding factors.

15 Let me just run through very quickly the sort of the
16 major areas that we talked about and ask you about whether
17 there are studies with respect to each of them that did sort of
18 control for polydrug use.

19 Verbal memory?

20 A. They have investigated it, yes.

21 Q. They have controlled for polydrug use?

22 A. They have investigated the effects of polydrug use and find
23 the deficits despite controlling for polydrug use.

24 Q. Is the same true for prospective memory?

25 A. I believe Heffernan has controlled for that, yes. And the

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0C7UMCC3

Parrott - redirect

1 Reneman study had co-use of cannabis as a co-variant because
2 they were heavy users of cannabis, and in Reneman they
3 controlled for co-variants but the deficits still remained with
4 respect to memory, yes.

5 Q. Executive function?

6 A. I am sure there have been studies. I can't recall --

7 Q. I think that you were asked on cross-examination about the
8 Fox study. Could you just explain the methodology of Fox and
9 what was actually found in that study?

10 A. Fox et al., 2001 I have already talked about. This is Fox
11 et al., 2002. And she had the very good idea of comparing the
12 cognitive profiles of Ecstasy users versus those with brain
13 damage. And so she linked to Barbara Sahakian from Cambridge
14 University who had given the CANTAB, Cambridge Automated
15 Neuropsychological Test Battery to various groups of brain
16 damaged patients at Cambridge University. And they had
17 different profiles for people with different areas of brain
18 deficits.

19 And when Helen did her 2002 study published in
20 Psychopharmacology, she found the deficits of the Ecstasy users
21 were similar to those with temporal lobe damage. That is the
22 area of the brain which was the side which was responsible for
23 memory, closely linked with hippocampus action. But she didn't
24 find deficits in tasks, frontal deficits, which we had expected
25 but that didn't occur in that study.

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(212) 805-0300

0C7UMCC3

Parrott - redirect

1 Q. But she did find some deficits?

2 A. She found deficits similar to those with people with
3 temporal lobe brain damage, yes.

4 Q. Counsel asked you about your 2006 review paper?

5 A. Yes.

6 Q. In that paper, counsel sort of related that you had
7 provided some examples in that paper of evidence showing lack
8 of impairment?

9 A. Right. In the 2006 review.

10 Q. But did you cite studies in that paper showing impairment?

11 A. Oh, yes.

12 Q. So really what was the purpose in writing the paper?

13 A. It was to try to look at some theoretical reasons why we
14 have such variance in findings. As I think I mentioned
15 earlier, a lot of the papers could be explained in terms of
16 whether people were light or heavy users and, also, the
17 co-various drugs were often modulated for findings in very
18 complex ways.

19 Q. The cognitive deficits that we have talked about this
20 morning, would they have an effect on people's everyday lives?

21 A. I am afraid so, yes. I have mentioned the prospective
22 memory. If I can give a sort of case report --

23 Q. Can I just ask, because counsel related that some of the
24 findings were that there was significant impairment,
25 significant statistically, but still within normal range.

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(212) 805-0300

0C7UMCC3

Parrott - redirect

1 A. Right.

2 Q. Can you comment on that?

3 A. If I can give an example, in 1999, when we were still at
4 the early stage of doing these studies, we had someone phone up
5 the laboratory and said they wanted to be tested. My research
6 assistants were busy and they could only come in the evening,
7 so I stayed behind at the office and met this Ecstasy user and
8 his girlfriend. And he was very interesting. I ended up
9 interviewing him for a couple of hours.

10 He was a regular user of Ecstasy, had used for a
11 couple of years and he then went on holiday, and he used
12 Ecstasy every night, and he took it and partied.

13 I don't know if I am allowed to swear in court, but he
14 said to me, "I woke up one morning and realized that I had
15 fucked my brain up" -- direct quote.

16 I said, what do you mean by that?

17 He said, well, I just couldn't remember anything. And
18 he said, I was really scared. And over the ensuing days, my
19 memory came back. But since then I have not taken Ecstasy.

20 I said, how long ago was that?

21 He said nine months.

22 I said, why did you come to see us today?

23 And he said, well, my girlfriend has been nagging me
24 to see somebody because he kept on having these severe memory
25 lapses.

SOUTHERN DISTRICT REPORTERS, P.C.

(212) 805-0300

0C7UMCC3

Parrott - redirect

1 And I said, why did you come to see me what made you
2 come?

3 He said, last week I was at a business meeting. And
4 he runs a music business with a friend and they had a business
5 colleague come and chat with them. And he said he greeted them
6 at the door, put out his hand, went to shake his hand and said,
7 hi, my name is - and he had forgotten his own name.

8 And he then said my name is Bob -- and he had
9 forgotten his own name -- which is a friend of his business
10 partner. So Bob looked at him, and the guy shaking his hand
11 looked at him and as he said to me, I didn't get the contract.
12 But he said, then I realized I had problems.

13 So I tried to interview him. I tried to offer him
14 help. I offered him to come back, but he wanted instant -- he
15 said, can you solve my problems? I want you to solve it?

16 I explained I couldn't. So if he had come back, I
17 would try to link him up with psychiatry and a therapy group,
18 try him with memory strategies, etc., but he didn't come back,
19 although I had urged him to.

20 That's the most severe example. And it was then that
21 I realized that these memory problems can be quite marked.
22 They were just not trivial. Some people are suffering.
23 Q. So does the fact that somebody's memory may still be within
24 the "normal" range, does not that mean it does not have any
25 practical effect on their practical day-to-day abilities?

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(212) 805-0300

0C7UMCC3 Parrott - redirect

1 A. Certainly in some people it does have practical adverse
2 effects. I also asked him about cannabis. He tried it and he
3 didn't like it. He said that the only drug he took regularly
4 was Ecstasy. He liked Ecstasy, but he wasn't a polydrug user.

5 MR. KOBRE: Just one more moment.

6 THE COURT: Take your time.

7 MR. KOBRE: Nothing further, your Honor.

8 THE COURT: Mr. Michaelman, do you have more than a
9 few questions on recross?

10 MR. MICHAELMAN: Not more than a few.

11 THE COURT: Then why don't you proceed now.

12 RE CROSS EXAMINATION

13 BY MR. MICHAELMAN:

14 Q. Dr. Parrott, just briefly, on the question of heavy users
15 which is discussed on the redirect, just because heavy users
16 are available for studies doesn't mean that whoever comes to
17 the studies is necessarily representative of users in the
18 population as a whole, correct?

19 A. Yes.

20 Q. Just to reiterate something you said on redirect, you
21 actually don't know what percentage of users are heavy users?

22 A. No.

23 Q. Finally, just on the issue of controlling for preexisting
24 conditions such as psychological problems, if a study has not
25 controlled for preexisting psychological problems and then test

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0C7UMCC3 Parrott - cross

1 users and then finds harms, we don't know whether the harm
2 comes from the use or the prior psychological problems, is that
3 fair to say?

4 A. Yes.

5 MR. MICHAELMAN: Thank you.

6 THE COURT: Anything further?

7 MR. KOBRE: No, your Honor, thank you.

8 THE COURT: Dr. Parrott, I have some questions for
9 you, but I think that I am going to put them to you after our
10 luncheon recess. Are you able to return after the luncheon
11 recess?

12 THE WITNESS: Yes.

13 THE COURT: Can we resume at 2:10, take a somewhat
14 shorter --

15 MR. MICHAELMAN: Of course, your Honor. I would even
16 be fine with starting at 2.

17 THE COURT: What about the defendants?

18 MR. RORTY: 2 o'clock is fine. That will help insure
19 that we conclude today.

20 THE COURT: Obviously, if it is necessary for us to
21 work beyond 5 o'clock to complete the hearing, we will do so
22 because I am sure that these folks have schedules and planes to
23 catch, among other things.

24 MR. CHUNG: That they do.

25 THE COURT: At this juncture, do the defendants

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0C7UMCC3 Parrott - cross

1 anticipate recalling either of your experts at the conclusion
2 of the government's presentation?

3 MR. RORTY: Not at this juncture, but that is subject
4 to Professor Hanson's testimony.

5 THE COURT: Then we will take an abbreviated lunch. I
6 will see you all at 2 o'clock.

7 You may step down.

8 (Witness excused)

9 (Luncheon recess)

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11 (Continued on next page)

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(212) 805-0300

0C74MCC4

Parrott

AFTERNOON SESSION

(2:00 p.m.)

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2
3 THE COURT: Dr. Parrott, prior to your engagement by
4 the government in connection with this matter, were you
5 familiar with the Sentencing Commission report to Congress in
6 2001?

7 THE WITNESS: No, your Honor.

8 THE COURT: You have reviewed the Sentencing
9 Commission report?

10 THE WITNESS: Right.

11 THE COURT: The Sentencing Commission placed
12 significant weight on studies by George Ricaurte. Have those
13 studies been discredited?

14 THE WITNESS: There was one study by Ricaurte in
15 Science which was retracted where he reported dopamine
16 neurotoxicity and that was retracted, yes.

17 THE COURT: Is there any other science that's cited in
18 the Sentencing Commissions report that does not hold true today
19 from your perspective?

20 THE WITNESS: No. I believe the main conclusions are
21 consistent.

22 THE COURT: In preparing for your testimony here, have
23 you become familiar with the sentencing guidelines?

24 THE WITNESS: I have had seen them, yes.

25 THE COURT: You understand that there is a methodology

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0C74MCC4 Parrott

1 utilized by the Sentencing Commission for determining
2 equivalent drug weights for the purposes of imposing sentence?

3 THE WITNESS: Right.

4 THE COURT: Do you recall in the report that the
5 Sentencing Commission said it shows a greater penalty structure
6 for MDMA than for powder cocaine?

7 THE WITNESS: Right.

8 THE COURT: The Sentencing Commission did so for three
9 principal reasons which I would like to ask you about. The
10 first reason that the Sentencing Commission proffered was, and
11 I will quote, unlike MDMA, powder cocaine is not neurotoxic.
12 Do you agree with that conclusion?

13 THE WITNESS: I have not studied cocaine so I can't
14 really answer that. I don't believe cocaine is neurotoxic, but
15 I have not looked at that literature.

16 THE COURT: In your work with MDMA have you become
17 familiar with the marketing of MDMA?

18 THE WITNESS: I have not really done research into
19 that, no.

20 THE COURT: The second reason that the Sentencing
21 Commission offered to Congress was that powder cocaine is not
22 aggressively marketed to youth in the same manner as MDMA. I
23 take it that you are not in a position to express any opinion
24 at all with respect to that point?

25 THE WITNESS: Yes, I cannot.

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0C74MCC4 Parrott

1 THE COURT: But can you tell me something about what
2 the age profile is for a typical MDMA user?

3 THE WITNESS: Typically late adolescence early
4 adulthood.

5 THE COURT: How does that compare to other drugs,
6 especially cocaine?

7 THE WITNESS: In the U.K. I think the target audience
8 is fairly similar.

9 THE COURT: The Sentencing Commission offered as its
10 third reason that powder cocaine is only a stimulant but MDMA
11 acts not only as a stimulant and a hallucinogen. Do you recall
12 reading that?

13 THE WITNESS: I read that, yes.

14 THE COURT: You heard Dr. Halpern's testimony
15 yesterday that the notion that a stimulant plus a hallucinogen
16 means something more than just a stimulant?

17 THE WITNESS: Right.

18 THE COURT: Do you agree that the fact that MDMA is
19 both a stimulant and a hallucinogen is a matter of significance
20 in comparing it to cocaine?

21 THE WITNESS: Its main effects are as a stimulant.
22 The hallucinogenic properties are really quite mild.

23 THE COURT: Would you characterize MDMA as a
24 hallucinogen?

25 THE WITNESS: As I say, it can have hallucinogenic

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0C74MCC4 Parrott

1 properties but they are very mild compared with the standard
2 hallucinogens. I would characterize MDMA as a stimulant and
3 energetic stressor rather than a hallucinogen. I think those
4 aspects are quite mild.

5 THE COURT: How many doses per gram are there in a
6 gram of MDMA?

7 THE WITNESS: How many tablets?

8 THE COURT: Yes.

9 THE WITNESS: In the U.K. it's thought to be around
10 about 70 milligrams per tablet.

11 THE COURT: Is that the average, about 70 milligrams?

12 THE WITNESS: That's the estimate.

13 THE COURT: As part of your work have you ever
14 conducted any chemical analysis on tablets to determine what
15 the weight composition of MDMA is?

16 THE WITNESS: No.

17 THE COURT: Does an Ecstasy user typically take only
18 one Ecstasy pill?

19 THE WITNESS: No. They take one as the first instance
20 typically, but then they typically increase their dosage. So,
21 regular users may well take 2 or 3 tablets. As they become
22 heavier they might take 6 tablets. Occasionally people take 10
23 or more.

24 THE COURT: Would they take those tablets all at one
25 time?

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0C74MCC4 Parrott

1 THE WITNESS: It varies. Generally they take them
2 successively. Heavy users might take a couple of tablets to
3 start with then one a few hours later, one after that
4 successively. They also take MDMA powders, particularly if
5 they are experienced users. That's in a larger amount.

6 THE COURT: Can you tell me how many doses there are
7 in a gram of cocaine?

8 THE WITNESS: No, I am afraid not.

9 THE COURT: How about marijuana?

10 THE WITNESS: Again, I am not sure.

11 THE COURT: In determining the harm posed by MDMA, is
12 it appropriate in your view to consider emergency room visits
13 or deaths associated with the use of the drug?

14 THE WITNESS: Yes, that could be a factor, yes.

15 THE COURT: In your view is cocaine more dangerous or
16 less dangerous than MDMA?

17 THE WITNESS: The problem with cocaine is it's far
18 more addictive than MDMA. The problems of cocaine use is far
19 more apparent. It's basically what you see is what you get
20 with cocaine. You see problems. MDMA is a far more subtle
21 drug, so the dangers of MDMA are more pervasive on a wider
22 range of functions. But people will be impaired in various
23 things but it won't be as severe as many of the problems of
24 cocaine, particularly in terms of addictiveness. It's a
25 difficult question to answer.

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0C74MCC4

Parrott

1 THE COURT: I understand it's a difficult question; I
2 have to press you on it.

3 THE WITNESS: Right. We have done a recent survey
4 where cocaine use has become more prevalent in the U.K., just a
5 couple very small studies, very small end. We asked people,
6 cocaine users and Ecstasy users, the same set of questions. In
7 this study the damage and acute effects of the drugs are quite
8 similar. They both reported memory problems. But the midweek
9 problems were more marked in the Ecstasy users. I think MDMA
10 has more enduring effects over time, particularly in recovery.

11 But there is large literature showing cocaine is more
12 addictive and its addictive properties in that aspect make it
13 more problematic. Some of our Ecstasy users in the interviews
14 conveyed problems getting into work on Monday, stuff like that,
15 which you tend to get in connection with cocaine and with MDMA,
16 but it's duration of the recovery period.

17 THE COURT: Have you familiarized yourself with some
18 of the studies that have been submitted to the court showing
19 that the number of emergency room visits relating to cocaine
20 far exceed the number associated with MDMA?

21 MR. MICHELMAN: I have seen that literature. One
22 aspect of that is MDMA is often taken at raves and you often
23 get triage at raves so you have paramedics attending raves.
24 The burning man festival was mentioned earlier, so you have
25 medics there. It may well be a fair number of MDMA users visit

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0C74MCC4

Parrott

1 the paramedics then rest and then recover in that medical sense
2 which is possibly not recorded on hospital data. That may be a
3 factor; I don't know.

4 THE COURT: You mention in your testimony that MDMA's
5 properties may be enhanced by heat?

6 THE WITNESS: Right.

7 THE COURT: By being in a warm place?

8 THE WITNESS: Right.

9 THE COURT: Are there any studies that have compared
10 whether there is more MDMA use in a warmer climate or during
11 the summer as opposed to the winter?

12 THE WITNESS: I don't know those studies.

13 THE COURT: The defendants' experts have argued that
14 MDMA fatalities are rare. Do you agree with that?

15 THE WITNESS: Yes.

16 THE COURT: In determining the harm posed by MDMA, is
17 it appropriate to consider the potential for addiction?

18 THE WITNESS: Yes.

19 THE COURT: There was also reference to a study that
20 you conducted of ranking the drugs by the degree of harm and
21 would you just report to me what it was that you concluded in
22 that study about MDMA in comparison to cocaine?

23 THE WITNESS: Cocaine was ranked second. I ranked
24 MDMA fifth in that paper.

25 THE COURT: What were the other drugs you ranked if

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0C74MCC4 Parrott

1 you can recall from one up to five.

2 THE WITNESS: I would have to check the paper. It
3 included things like tobacco, CAT, which is a herbal stimulant,
4 methadrone I think was another one. I don't think we had
5 methamphetamine, but I can't recall anymore.

6 THE COURT: Dr. Curran testified that the prevailing
7 consensus regarding the neurocognitive effects of MDMA is that
8 MDMA causes relatively minor but statistically significant
9 neurocognitive effects. Do you do agree with that?

10 THE WITNESS: In light and moderate use the effects
11 are significant and quite mild; in heavy users they are
12 slightly stronger.

13 THE COURT: When you use the word significant there,
14 you are referring to statistical significance --

15 THE WITNESS: Yes, I mean --

16 THE COURT: -- or not. Tell me what you are referring
17 to.

18 THE WITNESS: Well, both. So, it is statistically
19 significant, but it does have everyday lifetime implications.
20 So, for instance, with respect to memory, if you are missing
21 appointments with your boss, your boss is not going to be too
22 happy, and so it has everyday implications. It may not be
23 major implications but it certainly is going to adversely
24 affect your lifestyle if you are missing a proportion of future
25 memory appointments.

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Parrott

1 THE COURT: Yesterday Dr. Curran analogized it to
2 having a grocery list with 30 items and forgetting one item --

3 THE WITNESS: Right.

4 THE COURT: -- at the end of the day and she
5 characterized that, let me characterize it as minimal. I think
6 she said that it fell within the normal range of functioning.
7 My question for you is do you agree with that analogy by Dr.
8 Curran that the cognitive impairments, while they are there and
9 they are statistically significant, they still fall within the
10 range of normal everyday functioning?

11 THE WITNESS: If I can cite and reply the Morgan study
12 that looked at former users. They controlled to record 8.5
13 items of information. The former Ecstasy users in that study
14 reported 4.5 items of information. That was a fairly
15 substantial relative deficit. Certainly interviewing Ecstasy
16 users, they do report practical implications of memory loss is
17 adversely affecting their everyday life.

18 THE COURT: Do you agree with Dr. Halpern's testimony
19 yesterday that the brain changes noted in MDMA users are
20 comparable to FDA-approved SSRIs?

21 THE WITNESS: No.

22 THE COURT: Can you explain why not.

23 THE WITNESS: I think that the deficits, if you got
24 these deficits in a prescription medicine, it would never be
25 passed. We focus on the neurocognitive. There are other

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0C74MCC4

Parrott

1 deficits. One thing we have not mentioned is sleep apnea. In
2 a study by McCann, she recorded an increase of sleep apnea in
3 young Ecstasy users and sleep apnea is traditionally a disorder
4 of middle-aged overweight predominantly males. And they found
5 it in young not-overweight Ecstasy users.

6 The thoracic surgeons involved in the study were not
7 surprised. They said serotonin is involved in the control of
8 breathing, including breathing during sleep. That's a genuine
9 practical problem for youngsters. It's not just cognition.
10 It's the Connors immune incompetence. It's the reduction in
11 efficiency of white blood cells, those sorts of things,
12 hormonal changes. MDMA is a very powerful drug; it affects a
13 whole range of neurotransmitters. We focused on serotonin. It
14 also stimulates dopamine and that has adverse effects.

15 So it's a very different drug from cocaine. It's very
16 different to quantify. The effects of MDMA are more subtle.
17 In my assessment they are more pervasive because of a general
18 lowering of cognition and bodily functioning. In a recent
19 study, Scully et al. published 2010, which was looking at hair
20 analyses primarily, we asked about happiness ratings in Ecstasy
21 users and they were lower than the controls. This fits in with
22 the earlier study of Parrott and Lasky whereas the weight
23 Ecstasy users take and you may feel better, paradoxically over
24 the week they feel worse because the positive effects last a
25 few hours, the negative effects last a few days.

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0C74MCC4

Parrott

1 If you've got a regular Ecstasy user their overall
2 moods are overwhelming. In the same study we found high stress
3 levels in Ecstasy users, self-reported stress. So this regular
4 stress, energetic stress of regular MDMA use is leading to a
5 range of subtle but damaging effects upon human functioning.
6 It's not just neurocognition; it's other everyday happiness,
7 sleep, occupational problems have been related, interpersonal
8 problems. Also when you become a heavy user, aspects of
9 dependency, people spend too much time.

10 In the conference paper in Australia, the conference I
11 organized in Australia this summer, there was a paper by a user
12 group. They reported financial problems, that they were
13 spending so much money on Ecstasy that when eventually they
14 quit in their mid to late 20s, they didn't have the money, they
15 hadn't got any savings because they had been spending their
16 money on Ecstasy over those period of years. As they became
17 tolerant, they were spending more and more of their money on
18 the drug. So it's a wide range of issues to consider.

19 THE COURT: There also has been testimony from various
20 witnesses about recovery. What is the prevailing consensus
21 regarding recovery of the brain in years following MDMA use?

22 THE WITNESS: This isn't really my area. I have been
23 reading this area before this meeting, so I am rather limited
24 on the papers. I have not really read the papers on recovery.
25 But talking to Valerie Curran at lunch, she said there were

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0C74MCC4

Parrott

1 papers indicating recovery. I am not really aware of those
2 papers. But I was more aware of the paper showing damage, the
3 Kish paper. I think that's something I would like to clarify
4 for myself.

5 THE COURT: On cross-examination today you talked
6 about studies and sample sizes where if there is a harmful
7 effect that's reported, it may be more likely that a smaller
8 study will be published than if a similar-sized study did not
9 show any harmful effects. My question is do you find that that
10 is true with respect to all drug studies?

11 THE WITNESS: I think that's true with any scientific
12 trial. If you have a small sample size, any journal is likely
13 to reject it; they like a larger sample size.

14 THE COURT: I appreciate that point. I am moving to
15 the next point which was that it's more likely that a smaller
16 sample-sized study would be published in a journal if it showed
17 a negative or harmful effect as opposed to a similarly sized
18 study that didn't showed such an effect.

19 THE WITNESS: There is a statistical reason for that
20 in that it's called the power of the effect. If you have a
21 small sample and you show an effect, that means you have a
22 genuine validity of that study to generate the finding. If you
23 have a small sample and you don't defect the effect, it may
24 well be because statistically there is not enough power in that
25 design. So there is a reason why you would have a biased

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0C74MCC4 Parrott

1 publication rate for small studies. They are more likely to
2 accept positive results rather than negative for that
3 statistical reason.

4 THE COURT: Thank you, Dr. Parrott. Do counsel have
5 any questions they would like to pose to Dr. Parrott in view of
6 the court's inquiry.

7 MR. MICHELMAN: We have a few, your Honor.

8 THE COURT: All right.

9 RECROSS EXAMINATION

10 BY MR. MICHELMAN:

11 Q. You mentioned that the 70 milligram dose was the usual dose
12 for a tablet?

13 A. Right.

14 Q. A human might begin with one dose or maybe over the course
15 of night take 2 or 3?

16 A. Right.

17 Q. So in terms of a measurement we have talked about over the
18 course of the last two days, milligrams per kilogram, what
19 would one tablet of 70 milligrams translate to in terms of
20 milligrams per kilogram in an average human?

21 A. I need pen and paper to work that out. Sorry, 70
22 milligrams, I guess 70 kilograms, an average person --

23 Q. 70 kilograms is about 150, 160 pounds?

24 A. Yes. We are bit smaller in Europe.

25 THE COURT: We supersize everything over here.

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0C74MCC4 Parrott - recross

1 Q. About 1 milligram per kilogram would be a typical human
2 dose?

3 A. Yes.

4 Q. The judge asked you about conclusions in the 2001 report
5 and whether they hold true. Some of the science there relied
6 on animal studies where the animals were given much higher
7 doses in terms of milligrams per kilogram; 10, 20 milligrams
8 per kilogram. Would you agree that those doses are no longer
9 representative of average human use?

10 A. If you use interspecies scaling, the standard
11 pharmaceutical formula, then the dosage would be within that
12 range. But there are some studies since that, I can't recall
13 the names, but a paper published in 2006 or 2007 by animal
14 researchers where they had used lower doses with animals and
15 they found deficits with the animals with lower doses.

16 Q. In terms of the propriety of the dosing, you are aware that
17 the principles of interspecies scaling used by Ricaurte and
18 others around 2001 have come under serious criticism?

19 A. I believe the same interspecies scaling formulas are still
20 used by the pharmaceutical industry today as they were then; I
21 don't think they have changed.

22 Q. In spite of criticism by Dr. Baumann of NIH?

23 A. I am not aware of that, my understanding.

24 Q. You mentioned with respect to the ER data that that might
25 be useful to consider in terms of the harms of MDMA but that we

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0C74MCC4 Parrott - recross

1 couldn't rule out the possibility that Ecstasy users would be
2 attended to by paramedics rather than emergency rooms?

3 A. Right.

4 Q. But that's just really speculation on your part?

5 A. It was a paper by Suy et al., a Dutch group who went to a
6 as massive Dutch rave in 1999. They had a triage, medical
7 triage. They treated about 150 people at the rave. I think
8 they reported that none of those people needed then to go to
9 hospital. So the triage of a rave was dealing with the
10 problems.

11 Q. Are there any studies then showing the degree to which
12 potential emergency room visitors out of an MDMA user
13 population would be diverted to triages at raves and then not
14 go to an emergency room?

15 A. I don't know of other systematic surveys. I just know that
16 it's a fairly common phenomenon at raves to have these medical
17 facilities.

18 Q. You mentioned the Morgan study to discuss cognitive
19 impairment. What is the date of that study?

20 A. Morgan, 2002, I think.

21 Q. On cross-examination you spoke highly of the NextC study
22 which was a large prospective human study in the Netherlands
23 published in 2007?

24 A. Thelma Schilt, yes.

25 Q. So that's a pretty good study?

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0C74MCC4

Parrott - recross

1 A. Yes.

2 Q. I believe that's where Dr. Curran got her one item out of
3 the grocery list of 30 words from?

4 A. I think in that study, I am not sure where she got the one
5 in 30; it may well be that study.

6 Q. The later human prospective study supports Dr. Curran's
7 conclusion that the effect would be as slight as one item out
8 of 30?

9 MR. KOBRE: Objection.

10 THE COURT: Sustained.

11 Q. Would the Schilt paper support the notion that an Ecstasy
12 user might only forget one item out of the list of 30?

13 MR. KOBRE: Objection.

14 MR. MICHELMAN: On what grounds.

15 THE COURT: No. Sustained as to form.

16 Q. Are you familiar with the Schilt study?

17 A. Yes.

18 Q. In your view would the Schilt study support the conclusion
19 that an MDMA user might forget only one item out of a grocery
20 list of 30?

21 MR. KOBRE: Objection.

22 THE COURT: Overruled. He talked about another study.

23 He talked about a study on direct and on my examination where
24 there were 8.5 items and an Ecstasy user only could remember

25 4.5. We have had testimony about this grocery list and it's in

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0C74MCC4 Parrott - recross

1 the study. I think he can comment on it.

2 MR. KOBRE: I think the witness testified that he
3 didn't really recall the contents of the Schilt study.

4 THE WITNESS: I do recall the Schilt study.

5 THE COURT: There we are.

6 A. The Schilt study involved youngsters, I think 16 and 17
7 year-olds, and they used 3 tablets. So, after 3 tablets, if
8 they have a memory loss of one word is quite impressive.

9 Q. But that's what the study showed?

10 A. Yes.

11 Q. My final question is about the possibility of long-term
12 cognitive impairment. You mentioned you believe Ecstasy does
13 cause functional cognitive impairment in individuals. You gave
14 us examples, some anecdotes from your own experience where
15 study participants might forget to turn up for studies or
16 forget their own names. Are there any studies supporting this
17 phenomenon or are you just relying on those anecdotes?

18 A. Again, the Morgan study which I cited earlier would be
19 empirical support.

20 Q. For long-term?

21 A. For long-term. These are former users who recalled on
22 average 4.5 items of information compared with the controls who
23 recalled on average 8.5.

24 Q. You would stand by that in spite of the Schilt study?

25 A. They are independent studies; they are unrelated to each

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0C74MCC4 Parrott - recross

1 other. They both have got their own function, yes. The Morgan
2 people had used a lot more Ecstasy.

3 Q. That's interesting. So would you consider the Morgan
4 participants heavy users?

5 A. They have been using, yes, I can't remember whether they
6 were users. I think it was just a one standard use group. It
7 was one group of former users.

8 Q. Had they been heavy users?

9 A. I can't recall their criteria in the paper.

10 MR. MICHELMAN: Thank you.

11 MR. KOBRE: Just one.

12 Q. Has the Morgan study been called into question at all or
13 been discredited?

14 A. No.

15 MR. KOBRE: That's all.

16 THE COURT: Thank you.

17 You may step down. You are excused.S.

18 (Witness excused)

19 THE COURT: Would the government call its next
20 witness.

21 MR. CHUNG: The government calls Glen Hanson.

22 GLEN ROY HANSON,

23 called as a witness by the Government,

24 having been duly sworn, testified as follows:

25 DIRECT EXAMINATION

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0C74MCC4 Hanson - direct

1 BY MR. CHUNG:

2 Q. Tell us about yourself; tell us about your education.

3 A. I have a PhD in pharmacology and toxicology that was
4 received at the University of Utah. I have a DDS degree, a
5 doctorate in dental surgery, that I received at UCLA. I did a
6 postdoctoral fellow at NIH in neuropharmacology. I am
7 currently a full professor, a tenured professor at the
8 University of Utah, director of the Utah Addiction Center,
9 senior advisor to the director of the National Institute on
10 Drug Abuse at NIH, which is the National Institutes of Health
11 in Washington, D.C.

12 Q. National Institute on Drug Abuse otherwise known as NIDA?

13 A. NIDA, that's correct.

14 Q. What other affiliations have you had with NIDA?

15 A. I was director of the division of neurobiology and
16 behavioral science research and I was the acting director of
17 the institute from 2001 to 2003.

18 Q. What is NIDA?

19 A. NIDA is a federal agency. It's one of the NIH institutes.
20 It has the charge or mission to fund research from very basic
21 molecular genetic-type of research all the way up to clinical
22 or translational research with the intent of identifying issues
23 and biologies and hopefully therapeutics that would be useful
24 in treating problems associated with drug abuse.

25 Q. Is it true that NIDA is the single biggest funding source

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0C74MCC4 Hanson - direct

1 for those subject areas that you just catalogued?

2 A. That's correct. NIDA funds approximately 85 percent of the
3 research that relates to substance abuse in the world.

4 Q. What are your general areas of research?

5 A. My particular specialty are the psychostimulants in
6 particular. We research amphetamine or phenylethanolamine
7 drugs. So that would be amphetamine, methamphetamine, MDMA or
8 Ecstasy, and analogs associated with those drugs. We also look
9 at cocaine and we have done research on PCP, heroin, and we are
10 also interested in some neurobiological things that relate to
11 diseases such as schizophrenia and Parkinson's Disease.

12 Q. When did you start researching MDMA in particular?

13 A. We became interested in MDMA in 1985, '86, when the first
14 epidemic of Ecstasy abuse was occurring that started in Europe
15 and had moved across the ocean. We were seeing a significant
16 use by young adult populations. Because of its apparent
17 relationship, molecular relationship to the amphetamines, we
18 were interested in what it might look like as pharmacology and
19 its short and long term effects on neurosystems.

20 Q. You have been researching MDMA for the last 25 years?

21 A. That's correct.

22 Q. Have you published any studies or papers relating to MDMA's
23 physical effects?

24 A. In 25 years I would hope we got something on it. Yes, we
25 have published 30 to 40 papers that have been in scientific

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1 peer reviewed journals.

2 Q. Are you yourself on the editorial boards or boards of any
3 peer reviewed journals?

4 A. Yes, I review for many of the top pharmacology and
5 neurobiological journals.

6 Q. As you probably heard there has been quite a bit of
7 testimony and questions about the sentencing guidelines here as
8 they relate to MDMA. Are you familiar with the sentencing
9 guidelines or just generally familiar with what they are?

10 A. I am. I read the document that you provided and I have had
11 previous experience with the process early on.

12 Q. Is that the May 2001 Sentencing Commission report regarding
13 MDMA drug offenses?

14 A. That's correct.

15 Q. Let's go over that report which you had an opportunity to
16 review. Have you ever, did you ever testify in front of the
17 commission or Congress regarding this very topic, MDMA drug
18 offenses?

19 A. I have testified concerning the effects of MDMA, its
20 pharmacology and the status of the science at the time.

21 Q. When was this?

22 A. This was 2001 and 2002.

23 Q. There are a couple, a handful of excerpts that I am going
24 to read almost word for word. I ask you to comment on them.
25 On page 8 of the document, the first full paragraph, and the

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1 third sentence of that paragraph:

2 A comprehensive review of the scientific literature
3 reports findings from multiple scientific studies describing
4 symptoms of acute toxicity from MDMA use, including mental
5 status changes, hyperthermia, and other symptoms associated
6 with a serotonin syndrome.

7 That a was long sentence, but do you agree at the time
8 in 2001 that that was statement was true?

9 A. Yes.

10 Q. How about now; is that statement true?

11 A. Yes.

12 Q. What is a serotonin syndrome?

13 A. A serotonin syndrome is, as syndromes go, a constellation
14 of effects that could be caused because of a serotonin system
15 that is, I wouldn't say nonfunctional but it's functioning in
16 an abnormal way. In this case it is likely because of enhanced
17 serotonin action, and so serotonin systems throughout the body
18 are doing things that under normal physiological conditions
19 they wouldn't be doing and can associated with cardiovascular
20 responses, with pulmonary responses, or with responses in the
21 brain.

22 Q. Serotonin syndrome, in other words, it's not just one
23 thing, but as you said, it's a constellation of effects on the
24 body?

25 A. That's correct.

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1 Q. Let's goes over what is in that constellation. Let's start
2 with hyperthermia. Can you describe how MDMA relates to
3 hyperthermia or causes hyperthermia?

4 A. Serotonin pathways are important in the thermal regulatory
5 process, probably to the hypothalamus. The hypothalamus is a
6 center of controlling autonomic systems. Autonomic systems are
7 those that respond to environment. They help the individual
8 body adapt to the environment.

9 Q. Is the hypothalamus part of the brain?

10 A. Yes, it is. So something that disrupts serotonin which has
11 input into the hypothalamus, one could imagine would interfere
12 with how the body adjusts to the environment and that would
13 include temperature. So when we talk about hyperthermia caused
14 by drugs like MDMA and actually the same sort of thing happens
15 with other amphetamines as well, so it's not unique in that
16 property. But what happens is if you are in a hot environment
17 the body has difficulty cooling down because that thermal
18 regulatory system has been interfered with, so the body
19 temperature goes up, and if it's not dealt with, it can be
20 became fatal or at least it can become pathologic.

21 Q. Based on your understanding of MDMA use and MDMA's physical
22 effects on the body, why is it significant that hyperthermia is
23 experienced in hot or elevated temperature situations?

24 A. I am not quite clear, why is it significant in terms of
25 what happens to the person?

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1 Q. Yes.

2 A. Well hyperthermia when it's mixed with Ecstasy or MDMA,
3 this is a combination that results in the traditional serotonin
4 damage that has been associated with Ecstasy use. If you don't
5 have hyperthermia, then you don't see serotonin damage. It's
6 pretty much that simple. In fact, in laboratory animals, if we
7 take animals and put them in a very cold environment and we
8 expose them to very, very high doses of serotonin, you don't
9 get serotonin toxicity or damage. So, one would suspect that
10 the same thing applies to humans, that is, the higher the
11 environment, the higher the body temperature, the more
12 sensitive the individual becomes to the effects of MDMA and its
13 potential consequences on neurosystems.

14 Q. Based on your research of MDMA do you have an understanding
15 as to whether there is a typical setting in which MDMA is used?

16 A. It's typically used or certainly commonly used in the rave
17 setting or the club scene where there is lot of dancing,
18 temperature oftentimes is elevated, and there is physical
19 exertion and heat that's generated by all of the bodies and by
20 the increased motion and activity of the individual.

21 Q. Let's move on to another effect that you testified was part
22 of the serotonin syndrome, cardiovascular effects. What sorts
23 of cardiovascular effects are included in this serotonin
24 syndrome?

25 A. Serotonin also again through the hypothalamus and other

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1 mechanisms can alter the sympathetic nervous system. In the
2 case of MDMA, you not only have the serotonin piece, but you
3 also have the norepinephrine piece which is a critical factor
4 in sympathetic systems. For this reason you see a fairly rapid
5 and significant increase in blood pressure, in heart rate, in
6 pulse, the beats, number of beats per minute of the heart, and
7 as I said, this occurs fairly quickly to a level where you
8 would describe this person as being hypertensive if you didn't
9 know that they had been using Ecstasy.

10 Q. As a result of heightened blood pressure and pulse, what
11 kinds of ultimate cardiovascular effects have been observed?

12 A. They have seen arrhythmias, heart attacks, strokes that
13 have occurred in individuals that have used Ecstasy.

14 Q. Are effects on the liver part of the serotonin syndrome or
15 can they be?

16 A. It can be, yes.

17 Q. What kinds of effects have been observed on the liver in
18 connection with serotonin syndrome?

19 A. There has been damage to the liver, you have what they call
20 liver enzymes that show up when there has been damage that has
21 occurred. These liver enzymes can go up, suggesting that some
22 degeneration or problems have taken place in the hepatic
23 structure.

24 Q. One of the items listed in the 2001 report are mental
25 status changes. Can you elaborate on that being part of the

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1 serotonin syndrome?

2 A. Serotonin we know is a major role player in emotions and in
3 moods. Many of our antidepressant drugs base their therapeutic
4 efficacy on the fact that they change serotonin systems. Here
5 again it's not surprising if you have disrupted normal
6 serotonin functions, that it may have an impact on the mood
7 both in terms of when the serotonin comes out immediately after
8 you take the drug and then the consequences or what we would
9 call a withdrawal or rebound effect afterward.

10 Q. Another statement in the 2001 report, still on page 8, last
11 paragraph, first sentence: The potential toxicity to serotonin
12 neurons, however, has been the subject of some disagreement.
13 At the time in 2001, was that true in your observation?

14 A. Yes.

15 Q. How about now?

16 A. The disagreement piece?

17 Q. Yes.

18 A. Yes, there is certainly some disagreement.

19 Q. Potential toxicity of serotonin, I will cut to the chase;
20 we have been talking about neurotoxicity?

21 A. Correct.

22 Q. What is neurotoxicity?

23 A. Toxicity to neurosystems and generally we focus on the
24 brain as being an example; there could be other neurosystems as
25 well. My definition, I think a fairly generic definition of

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313

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1 toxicity implies that normal function has been compromised. If
2 it's an acute toxicity, it has been compromised for a short
3 period of time; if chronic, it's compromised for a long period
4 of time.

5 Q. Does neurotoxicity include, as you describe it, a potential
6 disruption in the production of serotonin?

7 A. That's true.

8 Q. Or some disruption in serotonin transporters or SERTs?

9 A. Yes, that would certainly be neurotoxic.

10 Q. Would neurotoxicity include disruption to the nervous
11 system itself?

12 A. Yes.

13 Q. How about what we have learned throughout the hearing as
14 axons; would neurotoxicity include effects on axons as well?

15 A. Yes, it would.

16 Q. What is an axon?

17 A. An axon is fiber process that comes from the cell body of
18 the neuron or the principal braincell and it extends to its
19 target in the brain, that's usually going to be another neuron,
20 and it's the business end of the cell, that is, its
21 responsibility is to make sure that the connection is to the
22 proper place, and then when what we call neurotransmitters,
23 these are chemical messengers that are released from the
24 neurons. They are managed at the end of the axon, a region we
25 call the terminal. They are managed both in terms of their

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1 synthesis, their turnover, their release, and their reuptake.

2 Q. The statement itself: The potential toxicity to serotonin
3 neurons however has been the subject of some disagreement. You
4 testified that you believe that was true back in 2001, the date
5 of this report, and that it's true today.

6 A. Correct.

7 Q. Could you describe the major issues in the disagreement as
8 to potential toxicity?

9 A. I don't think there is any disagreement about its potential
10 to cause neurotoxicity. That's very obvious. It happens when
11 you administer it to animals. That happens regardless what
12 species. Obviously you don't have studies where you are
13 allowed to go in and administer high doses of Ecstasy and then
14 go in and dissect the brain and do molecular analysis. We are
15 confined to using the tools that we have that won't inflict
16 harm or potential danger to the human and that's basically
17 imaging. Very crude, it's getting better, but it's still very
18 crude, and it restricts the kinds of questions we can ask about
19 the underlying mechanisms.

20 The bottom line is can Ecstasy be neurotoxic. It can.
21 It can be neurotoxic in a petri dish. If I were to just take
22 Ecstasy and put it on top of braincells, if they were serotonin
23 braincells, you would see a neurotoxic effect. It's even
24 neurotoxic if I were to put it directly onto tryptophan
25 hydroxylase which is an enzyme that synthesizes serotonin, it

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1 will decrease that activity and it will do it very rapidly.
2 And it does these things through an oxidating process. It
3 turns out that the amphetamines in general and Ecstasy in
4 particular has the potential to generate reactive oxygen
5 species.

6 Q. What is a reactive oxygen species?

7 A. It's a molecule that is looking for an electron or it is
8 oxidizing its targets and so what it does is it disrupts normal
9 molecular functioning, it can interfere with energy production,
10 it can damage DNA, genetic material. So if it's not controlled
11 and if it happens at a level that's too intense, it can
12 certainly compromise a cell's function or even in the extreme,
13 kill the cell.

14 Q. You testified earlier that neurotoxicity includes not just
15 disruption of serotonin, serotonin transporters, but
16 disruptions to the cell itself as well as the axon?

17 A. Correct.

18 Q. Has it been substantiated or at least suggested that MDMA
19 has an effect on the axon, the actual neuron?

20 A. The implication comes from evaluating the protein SERT or
21 serotonin transporter. As I said, it's a fairly crude way of
22 doing the analysis but at this point it's about the only way we
23 have. This transporter protein is only found in serotonin
24 neurons. So if the amount of the protein goes up or if it goes
25 down, we assume that changes have taken place inside of the

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316

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1 neuron, and we make an assumption that if it goes down, that we
2 have lost pieces of that braincell. I guess if it went up, you
3 would assume that we have gained pieces.

4 So it's a very simplistic analysis of quantitative
5 changes in that protein. We use that as our way of assessing
6 in live people whether their serotonin systems have been
7 changed.

8 Q. Give some examples of studies, preferably recent studies,
9 that have set forth that indication that you just described
10 that because of fluctuation in serotonin transporters, there is
11 a suggestion or an assumption that damage to the axons has been
12 done?

13 A. The more recent studies, they have been talked about
14 considerably up to now, is the Stephen Kish study where he
15 looked at, we call it a ligand, it's a molecule that
16 selectively binds to that SERT protein, and he observed in low
17 to moderate Ecstasy users that there were decreases in this
18 transporter in brain regions, the hippocampus and in some
19 cortical regions.

20 Q. Any other studies you can think of at this moment?

21 A. Well, there are a bunch of McCann studies which we talked
22 about. That group continues to do research and continues to
23 show those same kinds of changes. So there have been a number
24 of individuals who found that there are these shifts in the
25 transporter levels using brain imaging, path and SPECT imaging.

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1 Q. You are aware of the Netherlands NextC study?

2 A. Yes.

3 Q. You are familiar with a couple of the authors or
4 participants in that research?

5 A. The de Win, yes.

6 Q. Have you reviewed papers that have come out of the NextC
7 study?

8 A. Yes, I have.

9 Q. Have any of those papers spoken to this topic you just
10 described?

11 A. They have and they actually used some other strategies,
12 imaging strategies. They used MRS, magnetic resonance
13 spectroscopy. This is an imaging technique that looks at other
14 measures, more generic measures, not selective serotonin
15 measures, but they were interested in a measure of glial or
16 non-neuronal cell function. They were interested in also blood
17 flow, volume of blood flow where blood was going, and they were
18 interested in looking at measures of what we call light matter.
19 That would reflect myelin or non-neuronal or glial cells as
20 well. Then they did, they also did a SERT ligand with the
21 serotonin transporter.

22 Q. Is that similar to what happened in the Kish study?

23 A. It's a different ligand. It's been an issue of how
24 selective these ligands are, do they only bind to the serotonin
25 or do they bind to other targets or what is the background

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1 noise. Some of these earlier ligands were fairly noisy, so it
2 was hard to pick out what was selective binding and what was
3 just nonspecific binding.

4 Q. To be clear, a ligand is basically a tool for researchers
5 that will show, that will attach to serotonin transporter
6 chemicals?

7 A. Correct. Then the ligand has a radioactive emitter so that
8 you can pick it up on your imaging technology and you can see
9 where it is so you get a single vision of intensity that has an
10 anatomical component to it so you can see where and quantify.

11 Q. Another statement in the 2001 report, page 9, the first
12 full paragraph, second sentence, this is an observation from
13 one particular research study: The brain scan comparison of
14 MDMA users with nonusers indicated that users had a
15 significantly reduced number of serotonin transporters
16 throughout the brain and that the magnitude of the loss was
17 associated with greater use of the drug.

18 That's a statement in 2001?

19 A. Correct.

20 Q. Are you aware of studies that came to this particular
21 observation back in 2001?

22 A. Probably mostly based on the McCann studies.

23 Q. How about today, have there been studies that have observed
24 these particular phenomena?

25 A. Again, I think they have been cited. There tends to be

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1 this dose response phenomenon, that is, the heavy users, the
2 more intense the history of using Ecstasy, the greater the
3 likelihood of seeing these markers change, and one would
4 suspect that the longer the duration of the change, whether
5 it's permanent or not, but those discussions are still being
6 had.

7 Q. You predicted the next excerpt in the 2001 report, page 10,
8 first full paragraph, first sentence: Another point of
9 controversy surrounding the MDMA research literature is whether
10 loss of these serotonin sites and corresponding impairment is
11 permanent.

12 Back in 2001, I know you have had a chance to read
13 this 2001 report, did that point of controversy actually exist?

14 A. It did.

15 Q. How about now?

16 A. It still exists.

17 Q. Describe just the nature of the controversy; what are
18 people talking about here?

19 A. Well, in some cases they are comparing apples and oranges,
20 so on one hand there is the discussion about the recreational
21 use and almost by definition that means low dose, 1 to 2 tablet
22 kind of use where you are getting maybe 1, 1-1/2 milligrams per
23 kilogram of the drug versus intense use where somebody maybe is
24 taking 4, 5 tablets, getting up to around 5 milligrams per
25 kilogram of the drug.

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1 And those two groups may present in very different
2 ways and it's going to be a sliding scale. It's not going to
3 be black and white. You are going to find a lot of gray
4 between those extremes and that gray is going to vary on a
5 number of principles, for example, the environment. I already
6 mentioned that whether there is damage or not depends a lot on
7 how high the body temperature goes.
8 That's going to be dependent on the environment,
9 whether it's an environment that's got an air conditioner and
10 all the windows are open and you are in the mountains and there
11 is a cool breeze or whether you are in downtown New York in the
12 middle of the summer and the air conditioner is gone. So
13 that's going to change.

14 (Continued on next page)

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1 A. So that is going to change and then it is also going to
2 change also based on other factors like are there other drugs
3 in the body, is the individual bringing other vulnerabilities
4 to the issue or the experience.

5 We are not talking about genetics, and genetics have
6 not really been studied relative to MDMA very much, but it
7 certainly has relative to methamphetamine toxicity, and
8 genetics seems to play an important role. And my guess is that
9 it is playing that role here.

10 So there are a lot of variables that are happening.
11 And at the end of the day, you get a group of people who are
12 low users and you don't see a significant change. And you say
13 the drug seems to be not particularly dangerous.

14 And somebody else gets another group, just as
15 legitimate research, but all of these other potentiating
16 factors are in place and they see a change and they say, look,
17 it has the potential for causing some significant damage.

18 Q. Now, the point of controversy here is identified in that
19 sentence was, whether the loss of the serotonin sites, the
20 neurotoxicity and the impairments were permanent.

21 At the time of the 2001 report, was there evidence or
22 was evidence offered that neurotoxicity and those impairments
23 were temporary?

24 A. I would say more could be permanent or could be temporary,
25 again, based on what your subjects look like.

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1 At the time we had somewhat limited -- I shouldn't say
2 limited -- we had been looking at the drug for almost 15 years
3 in this country, but still is 15 years permanent? Is 20 years
4 permanent? It depends how long you live as to what permanent
5 is and how permanent is defined.

6 The implication, the data that was present suggested
7 that it was going to be long lasting in some users. Whether
8 you call that permanent or not, it certainly seemed to be a
9 possibility for some people.

10 Q. But is it fair to say that there were studies or data at
11 the time in 2001 that in certain relatively lower dosages, the
12 effect of the neurotoxicity and the impairment was not long
13 lasting?

14 A. Yes. There was discussion on both sides. There was
15 discussion, look at some, it seems to be long and even profound
16 and in others it seemed to be minimal and temporary.

17 Q. I am going to go back in this report to page 8, last
18 paragraph, second sentence: A leading researcher in MDMA
19 toxicity studies and the focus of some of the controversy has
20 performed numerous studies on both animals and humans and,
21 again, I will cut to the chase. That researcher is George
22 Ricaurte.

23 Do you know George Ricaurte?

24 A. I do know Dr. Ricaurte.

25 Q. And do you know that the Sentencing Commission did consider

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1 his research in deliberating over the sentencing guidelines?

2 A. Yes, they did.

3 Q. Are you aware of a study or a publication by Dr. Ricaurte

4 and his research team entitled "Severe Dopaminergic

5 Neurotoxicity in Primates after a Common Recreational Dose

6 Regimen of MDMA," published in Science in 2002?

7 A. I am.

8 Q. Have you reviewed that particular publication?

9 A. I have certainly read it in some detail.

10 Q. Were you acting director of NIDA at the time that that
11 publication was issued?

12 A. I was.

13 Q. Are you aware that that publication was retracted?

14 A. Yes, I am.

15 Q. When you first read the publication -- actually, was it in
16 published form when you first read it?

17 A. I may have seen a preprint of it. I can't remember, but it
18 was soon after it was published if not just before.

19 Q. What was your reaction to it?

20 A. It did not correspond with my experience researching this
21 drug.

22 Q. Can you just tell us generally what the article and
23 publication was about?

24 A. Well, it talked about Ecstasy also being a dopamine toxin
25 and this comes from the fact that methamphetamine which is

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1 chemically related. MDMA stands for
2 methylenedioxymethamphetamine. So it is a methamphetamine
3 analog.

4 Methamphetamine damages both serotonin and dopamine,
5 so Dr. Ricaurte was reporting that in his research he was
6 seeing some dopamine damage along with the serotonin damage.

7 And we had looked at this a number of times and had
8 never seen any hint of dopamine damage. Others such as Bryan
9 Yamamoto had also looked at it several times and had never seen
10 any damage to the dopamine system.

11 So I was -- let's say healthy skepticism was my
12 reaction to it.

13 Q. Now, you had a chance to review the 2001 report. Is
14 neurotoxicity to dopamine or its related processes mentioned
15 anywhere in the 2001 report?

16 A. No.

17 Q. But you did testify, is it true, though, that MDMA use has
18 an effect on dopamine?

19 A. It is.

20 Q. Can you describe that effect?

21 A. MDMA is what we call a releasor molecule in contrast to
22 serotonin selective uptake blockers which are uptake block
23 inhibitors. Cocaine is an uptake block inhibitors. The
24 amphetamines are releasors, so their mechanism is very
25 different.

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1 Both kinds of drugs will result in an increase of the
2 transmitter serotonin and dopamine. Increase in those
3 transmitters outside of the cell and the message that they send
4 will be augmented, but they do it in very unique mechanisms.

5 With MDMA, what it does is, it disrupts the storage of
6 the serotonin inside of the cell. The serotonin is stored in
7 little packages we call vesicles. And these vesicles have
8 proteins on them called vesicular monoamine transporters.

9 And these transporters take the serotonin, once it is
10 produced, and put it inside the vesicles. And this is done for
11 two reasons. One is that it prepares it so that if that brain
12 cell is stimulated, the vesicle will then traffic to the
13 terminal and dump out the serotonin and the serotonin can exert
14 its effect.

15 But also it does it because serotonin has the
16 potential of becoming an oxidative problem for the system. So
17 by packaging it and keeping it inside, you sort of protect it
18 and prevent it from doing this molecular explosion.

19 Q. Does MDMA have the same type of mechanical effect on
20 dopamine or is it different?

21 A. Both of them, it does it to dopamine and it does it to
22 serotonin.

23 Q. You described to us in the context of serotonin syndrome
24 how that release of serotonin affects various bodily systems.
25 How does the release of dopamine affect various bodily systems,

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1 if at all?

2 A. It does. It is important to keep in mind that the
3 relationship between the two exists, that is, that the MDMA
4 causes about 10 times more serotonin to come up than it does
5 dopamine.

6 So a comparison to methamphetamine, methamphetamine is
7 more of a one per one. That is why Ecstasy is more selective
8 to the serotonin system, whereas methamphetamine hits both
9 dopamine and serotonin. So Ecstasy does cause the dopamine to
10 come out.

11 Q. What happens when the dopamine comes out?

12 A. It activates its receptor targets. This is probably the
13 basis for some of the euphorogenic properties of the drug --
14 the stimulation, the energy, the enthusiasm. And it also tends
15 to be the basis for the addiction process for drugs of abuse in
16 general.

17 Q. As you probably heard by now, addiction is a hot button
18 issue here?

19 A. Yes.

20 Q. You testified that dopamine is related to the addiction
21 properties of drugs?

22 A. Correct.

23 Q. Does the MDMA effect on the dopamine system have any
24 relationship with the addictive properties of MDMA, if those
25 addictive properties exist?

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1 A. It would. It is confounded by the issue that there is this
2 disproportionate amount of serotonin that is coming out. And
3 what it looks like, the serotonin may get in the way of that
4 normal addiction.

5 So when you heard some equivocation on the part of Dr.
6 Parrott, well, it is not addicting as, say, cocaine or some of
7 those other stimulants of abuse -- at least not at the onset it
8 doesn't appear to be. But as the person continues to use it
9 over extended periods of time, especially if they start
10 escalating in dosages, then the addiction key start to show up
11 more and more.

12 And we think what is going on is, this reflects a loss
13 of some of the serotonin influence because the serotonin seems
14 to trump the dopamine when it is so disproportionate. But as
15 you lose some of that serotonin action, then the dopamine
16 effect becomes more dominant. And at that point the drug
17 experience is likely or more likely to go on to become an
18 addictive exercise.

19 Q. Just to be clear, is your testimony or your observation
20 that, upon initial use of MDMA, the serotonin release is
21 proportionally larger, as you say, 10 times larger than the
22 dopamine release, correct?

23 A. Correct.

24 Q. And the dopamine release, typically, for drugs, is related
25 to the addictive properties of the drugs?

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1 A. Yes, that's true.

2 Q. Because in the beginning with the initial use of the drug,
3 the serotonin release is greater than the dopamine release, you
4 don't see necessarily an addictive property to the drug,
5 correct?

6 A. Right. Certainly it is minimized.

7 Q. So let's stop there. You went on to describe a second step
8 in the serotonin, the effect on serotonin in the drug. What is
9 that second step?

10 A. Well, you mean in terms of, as the serotonin influence
11 starts to deteriorate and the dopamine influence starts to
12 increase?

13 Q. Exactly.

14 A. So that brings with it -- that is associated with the
15 reward pathways, what we call the mesolimbic pathways. And
16 these are almost always involved in energizing that addictive
17 process, where the person is inclined to do it over and over
18 and over again.

19 And then you start to get some subtle changes in the
20 dopamine system that can take you into a very compulsive
21 behavior. And you use the drug and sort of the general
22 definition of addiction is that you are so compulsive about
23 using the drug that you disregard all the negative consequences
24 that are resulting.

25 And this is an extreme position of addiction for

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1 someone that has Ecstasy. It happens. Certainly doesn't
2 happen as often as with cocaine or, say, with the heroin, but
3 it happens as Dr. Parrott was mentioning.

4 Q. Are there any other features -- there has been a lot of
5 comparison between cocaine and MDMA, especially with respect to
6 addiction. Are there any features of cocaine use versus MDMA
7 use that may also contribute to the differences in the
8 addiction properties?

9 A. Well, the cocaine, it doesn't have that disproportionate
10 piece between the serotonin and the dopamine influences. They
11 are more of a one-to-one relationship, and they may even be
12 more on the dopamine side than on the serotonin side.

13 So you don't have to suppress the serotonin in order
14 to allow the dopamine effect to express itself. It is going to
15 be there. It is going to be there from the first exposure to
16 the drug.

17 Q. Is there anything about how these respective drugs are used
18 or administered that relates to the addiction properties of the
19 drug?

20 A. What we call the pharmacokinetics, and this has to do with
21 how a drug is administered, how it distributes, where it goes
22 once it gets inside of the body, how it is metabolized and how
23 it is eliminated.

24 Those are different for these two drugs. The Ecstasy
25 is typically taken orally. And, usually, an oral drug is less

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1 likely to be addicting than if you took that drug and you
2 injected it IV or if you smoked it.

3 Q. Why is that?

4 A. It has to do with how quickly the drug gets into the brain
5 and how much of it gets into the brain at one time. If you are
6 smoking, say, like crack cocaine or you are IV-injecting crack
7 cocaine, it gets into the brain in a matter of seconds. When
8 it hits the brain, it hits it in a very high concentration, so
9 the effect on the dopamine system is abrupt and it is fairly
10 dramatic.

11 With Ecstasy you are taking it orally. It goes into
12 the gut. It has to diffuse across the lining of the gut, and
13 the intestines, gets into the bloodstream goes into the liver.
14 Some of it gets metabolized, makes it way up to the heart.

15 Eventually it gets up to the brain. And when it gets
16 there, generally, the concentrations of the drug will be
17 diminished, so it doesn't hit the brain in this one bolus like
18 you would see with cocaine.

19 Q. Do you know whether Ecstasy is consumed in ways other than
20 just an oral administration?

21 A. An oral administration is by far the most common use.
22 Occasionally you hear of people who try to snort it, and I am
23 sure that there are people who inject it intravenously, but
24 that is fairly unusual.

25 Q. You have had a chance to review a document dated November

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1 22, 2010 that contains, in essence, summaries of proposed
2 testimony by the defense's experts, correct?

3 A. Yes.

4 Q. Dr. Curran and Dr. Halpern?

5 A. Yes.

6 Q. I want to read a handful of excerpts, and I would like to
7 ask you for your reactions and general comments.

8 A. OK.

9 Q. We will start with Dr. Curran's proposed testimony or a
10 summary. "Many of the early studies in MDMA failed to account
11 for confounding variables such as polydrug use, psychological
12 history and biased self-reporting." Was that true back in 2001
13 with those early MDMA studies?

14 A. They probably didn't ask those questions very much then,
15 and they are asking them now. So in terms of attitude, one
16 could say yes, that's a little different.

17 Q. Polydrug use, a confounding factor that has been discussed
18 during this hearing. Can you comment on the significance of
19 polydrug use in the study of MDMA?

20 A. It is known that the vast majority of MDMA users are
21 polysubstance abusers. And so I guess I find it interesting
22 that we are so concerned about what does MDMA do all by itself
23 when in fact, in reality, that's not going to be very
24 practical.

25 In reality, the vast majority of the users are going

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1 to have these other drugs on board, so probably a more relevant
2 real time question is, what does Ecstasy do when these other
3 drugs are on board. So I think that that's a factor, but there
4 have been some studies that have been done that have tried to
5 sort that out.

6 Does Ecstasy really bring some potential problems in
7 that sort of an environment?

8 Here, again, the answers have been somewhat equivocal.
9 There have been those who have said no. When we factor out the
10 polydrug use, the Ecstasy, the common theme that seems to be
11 present in all of these is causing an effect.

12 And then other studies have said, well, when we factor
13 out the polydrug use -- or the polydrug use itself seems to be
14 causing some of these effects. So that minimizes the
15 contribution of the Ecstasy.

16 Q. How about psychological history as a confounding factor in
17 these studies? What is the significance of the preexisting
18 psychiatric conditions in MDMA users?

19 A. Here, again, this is a very critical real life issue that
20 has to be addressed because it is true that a lot of these
21 people bring with them psychological baggage.

22 And here, again, I find it somewhat interesting that
23 as investigators we lean over backwards to make sure that we
24 clean up our sample and get rid of all of the underlying
25 psychiatric issues. Those are exclusionary criteria. If you

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1 have depression or you have some significant psychological
2 history, we don't want you to participate in this. When in
3 reality, these are the people that are using the drug and
4 exposing the drug.

5 And one would suspect that the interaction between the
6 pharmacology of the Ecstasy and the underlying pathology of the
7 psychiatric disorder are probably going to interact and create
8 problems for these people.

9 Q. Another sentence or another excerpt from the summary:

10 "According to the best recent studies of the effects of MDMA in
11 humans, the drug's effects are relatively mild and not
12 permanent." What is your reaction to that?

13 A. Well, I guess the definition of "mild" is in the eye of the
14 beholder. I had to smile when we had the discussion about you
15 forget 1/30th of these names or words. Well, what if you are
16 at the party and there are 30 people there and the name that
17 you forget is your boss? That becomes pretty critical.

18 So if you are not always selective as to which are the
19 1/30th of the words you get to forget nor are you able to
20 select when you forget them, so any compromise of your ability,
21 whether you call it subtle or dramatic, can be pathologic, can
22 prevent you from getting that raise, can make you less
23 competitive in a very competitive world.

24 So for one person that is a farmer and not talking to
25 anybody, in a very simplistic world, maybe you can get by with

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0C7UMCC5 Hanson - direct

1 that and it is not going to change your life. But if someone
2 is trying to function in the corporate world of downtown New
3 York, that can be a very critical issue.

4 I struggle a little bit with, a little bit of deficit
5 isn't a big deal and we should be happy with that, but I am not
6 sure that we should ever be happy with losing function.

7 Q. Well, your reaction to that statement was in terms of
8 function, right, not memory losses, name or other things in
9 real life?

10 A. Right.

11 Q. And I think this is your area of expertise. What about the
12 biological effects? Do you agree with the statement that, as
13 it applies to biological effects, that the effects of MDMA are
14 relatively mild biologically?

15 A. Well it comes back to the issue of how do you define
16 "minor," how close are you to the edge and how far do you have
17 to be pushed before you go over the edge. If you are
18 biologically a long ways from the pathologic edge, yeah, you
19 can afford to be pushed a little bit towards it. But if you
20 are right on the edge and you go over --

21 Let me just give you an example. A lot of the
22 discussion I have heard today, I have heard before relative to
23 methamphetamine. We had some of the same discussions about
24 methamphetamine back in the '70s and the early '80s for some of
25 the same reasons, methodological reasons. And we found that we

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1 were one of the first groups to find that there is this
2 dopamine deficiency that occurs in laboratory animals, and it
3 took almost to the latter part of the '90s to confirm that in
4 humans.

5 And then the question is, you only see like a 10 or 20
6 percent deficit in the dopamine system in humans, how big of a
7 deal can that be?

8 Well, we just found with a study that is going to be
9 published that it is big enough that we are finding those who
10 have a history of methamphetamine dependence are five times
11 more likely to become Parkinsonian patients.

12 So it is only a 10 or a 15 percent push down a road
13 that leads to degenerative pathology that shows up later on in
14 your life. So 10 percent when you are 30 doesn't seem like
15 much, but 10 percent when you are 60 and you are close to the
16 edge of Parkinson's, all of a sudden, that becomes very
17 critical.

18 So those are questions that are out there that we
19 haven't answered, but we have to consider.

20 Q. Next statement: The drug does result in impairment of
21 human user's verbal memory, but the drug's effects wear off
22 over time and deficits in brain chemistry do not persist.

23 Your reaction?

24 A. We have to keep in mind that, at least in the human
25 studies, we are using very crude methodology. All it tells us

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1 is, there are changes in the quantity and some of the
2 anatomical, but very crudely, the anatomical distribution of
3 that protein in the brain. That's all we can tell from our
4 imaging strategies.

5 Q. Has there been conclusive evidence that deficits in brain
6 chemistry do not persist?

7 A. I think there have been studies that say no, it doesn't or
8 that there is some recovery that occurs.

9 Q. Has there been conclusive evidence that full recovery
10 occurs from any dosage of MDMA?

11 A. That is a question that we can't answer yet, quite
12 honestly. We don't have the methodology in humans to answer
13 that question. So we can say, yes, it looks like on our scans
14 that the serotonin transporter levels come back to normal or a
15 normal range -- because you are always dealing with a range.
16 Does it come back to a normal range? And using the fairly
17 simplistic cognitive assessments that we typically use that the
18 function returns, we can say, yes, that happens.

19 But what we can't say is, we can't say does quantity
20 of the serotonin transporter mean that normal function has
21 totally returned? And normal function really reflects on how
22 do you survive in a very complex world.

23 And our assessments and our tests, usually they are
24 done in a very sterile environment. We put them a room. We
25 keep everything quiet, and we try to focus in and dissect out

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1 various pieces of cognition. But cognition doesn't exist in
2 isolation.

3 Maybe a better strategy would be to take them to work
4 and evaluate them under the various complexes of work and
5 pressures and demands on their time and how do you interact
6 with your family. And you look at the complex day-to-day
7 living issues and ask those questions, and those questions have
8 not been answered. They have not been asked.

9 Q. Let's move on to Dr. Halpern's section of this.

10 There is a statement in here that recent prospective
11 studies on humans have not found significant changes in
12 serotonin systems over time or evidence of permanent damage.
13 Do you agree with that statement?

14 A. Again, I think Dr. Parrott gave several examples of studies
15 that have shown that there are changes and those changes
16 persist for months. There are studies out there that say that
17 they persist for 10 years now.

18 Q. "Unlike cocaine, MDMA is not addictive." Do you agree with
19 that?

20 A. Well, we talked a little bit about addictive in a different
21 way. The mechanisms are different because of this very
22 prominent upfront serotonin piece that we see with Ecstasy.

23 Q. So do you agree with that or not?

24 A. I would certainly say it is less addictive in initial
25 exposure to the drug, yes.

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1 Q. But you testified earlier about how it becomes addictive?

2 A. To those that escalate their doses, yes.

3 Q. "Unlike cocaine, MDMA does not induce a breakdown of the
4 blood/brain barrier." Do you agree with that?

5 A. No. Most of your sympathomimetics will change your
6 blood/brain barrier. There have actually been a couple of
7 studies that have looked at MDMA, and it says it works pretty
8 much like other sympathomimetics, and it will break that
9 blood/brain barrier down.

10 Q. What is the significance of a breakdown of a blood/brain
11 barrier?

12 A. Well, the blood/brain barrier is supposed to be protecting
13 the brain from large molecules or from things that could damage
14 or interfere with the normal functioning of the brain. So if
15 you were to break that down -- let's say metabolic products
16 that are part of normal living. Well, they are not supposed to
17 get in the break because they muck up the system. So if you
18 break down the brain and these things start to get into the
19 brain, then they can interfere with how the brain works, and it
20 can cause things such as confusion or some of the mental issues
21 that we see associated with some of these drugs.

22 Q. There have been questions asked about relative harmfulness
23 of cocaine and MDMA. Can you state whether one drug is more
24 harmful than the other?

25 A. I won't state it again in the generic way, but if you

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1 became specific, that is, if you looked at the acute toxicity
2 on cardiovascular systems, how does that compare, you could
3 make a comparison.

4 We already talked about addiction. Cocaine upfront is
5 going to be more addicting than Ecstasy is.

6 Both of them, as sympathomimetics, can cause problems
7 with the cardiovascular system. They cause death.

8 There are individuals who have evaluated that and have
9 claimed that they are fairly similar in that property because
10 both of them enhance norepinephrine systems in quantitatively
11 similar ways, so arrhythmias, heart attacks, strokes -- those
12 kinds of things you would see somewhat equally between the two
13 drugs.

14 If you started to look at what we call cellular
15 neurotoxicity, cocaine tends not to be very neurotoxic to the
16 cells whereas, as I have already mentioned, Ecstasy itself, the
17 MDMA itself creates these oxidative events that are problematic
18 for the cell, and cocaine doesn't do that. And it goes back to
19 its basic mechanism whereas cocaine is an uptake blocker, its
20 functions are a lot like the serotonin selective uptake
21 blockers -- in fact they compete for the same site on the
22 protein in the serotonin system -- whereas Ecstasy, it goes
23 right into the cell. It alters the vesicle storage. And it
24 creates this problem for the cell in terms of how do we deal
25 with his reactive oxygen species.

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1 Q. Is it fair to say that cocaine and MDMA share certain
2 harms?

3 A. They do.

4 Q. And is it fair to say that cocaine has certain harms that
5 MDMA doesn't?

6 A. Yes.

7 Q. Is it fair to say that MDMA has certain harms that cocaine
8 doesn't have?

9 A. That's correct.

10 Q. Along the lines that you just detailed?

11 A. Yes. And I talked a little about tryptophan hydroxylase.
12 Cocaine doesn't do anything to tryptophan hydroxylase, whereas
13 you will see this fairly significant depression of this enzyme
14 over days. Usually it will come back, although in some cases
15 it stays down for longer periods of time.

16 Q. Just to be clear, that depletion of tryptophan has an
17 effect on serotonin production?

18 A. It does. Tryptophan hydroxylase is the enzyme that
19 synthesizes serotonin. So if your tryptophan hydroxylase isn't
20 functioning, then your stores of serotonin goes down and they
21 will stay down until you are able to replenish that enzyme and
22 restore its function.

23 Q. Based on your reading of the 2001 MDMA, the Sentencing
24 Commission report, were there any harms that the commission
25 forecast with respect to MDMA? Did it predict any harms?

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1 A. Well, I am not sure that it predicted specific harms other
2 than to say, generically, we need to be cautious. We are
3 concerned that there are trends here, and we need to be paying
4 attention to these trends as to the persistent effects of
5 Ecstasy in some users.

6 Q. Dr. Halpern has an excerpt in his summary: "Year after
7 year, studies of MDMA users failed to replicate the harms
8 forecast in 2001." Do you agree with that statement?

9 A. I am not sure what he is referring to.

10 Q. Like what?

11 A. As I said, I don't see that there were harms that they
12 predicted. I didn't ever read in that that there is this
13 epidemic of people who had total wipeout in their serotonin
14 systems and fill their psychiatric institutions -- there isn't
15 any kind of dire predictions like that at the commission.

16 Q. There is this ultimate statement from both Curran and
17 Halpern: "Today, no reasonable scientist aware of the
18 intervening scientific literature since 2001 could arrive at
19 the same conclusions espoused by the 2001 report." Do you
20 agree with that?

21 A. No, I don't -- well, I would hope that is not true because
22 that's kind of where I am. So I hope I am a reasonable
23 scientist.

24 Q. Are you the only one where you're at?

25 A. Well, I would say that most of the basic scientists that

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0C7UMCC5 Hanson - direct

1 work in this area would agree with me. Those of us who are
2 familiar with this molecule and how it works would still say,
3 this is a troubling molecule, and when it is released,
4 especially used by young people without any kind of discretion
5 or any kind of control -- and young people are attracted to use
6 this and, unfortunately, a lot of them think it is a fairly
7 innocuous molecule. We see potential problems with that kind
8 of a backdrop.

9 MR. CHUNG: No further questions at this time.

10 THE COURT: We will take a very short recess.

11 Dr. Hanson, will you step down for a few minutes.

12 We will reconvene in 10 minutes.

13 (Recess)

14 THE COURT: Cross-examination, Mr. Rorty.

15 CROSS-EXAMINATION

16 BY MR. RORTY:

17 Q. Good afternoon, Mr. Hanson.

18 We have talked over the last two days and you just did
19 in your direct testimony about the United States Sentencing
20 Commission 2001 report and its comparison of the harms of
21 cocaine and MDMA?

22 A. Yes.

23 Q. As you know, the commission believed at that time that MDMA
24 was more harmful than powdered cocaine, correct?

25 A. Yes. I would say that they inferred that, sure.

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1 Q. That was the commission's conclusion?

2 A. Right.

3 Q. And based on your reading of it, part of the basis for the
4 establishment of criminal penalties for MDMA?

5 A. Correct.

6 Q. What I understand from your testimony is that, as a
7 scientist, that comparison is, to some extent, apples and
8 oranges because there are different kinds of harms?

9 A. Right.

10 Q. In attempting to answer this question that interests
11 lawyers and judges about which is more harmful and how they
12 should be ranked, you simply approached that from a different
13 angle as a scientist?

14 A. That's correct, yes.

15 Q. That's because, first of all, they are different types of
16 drugs?

17 A. Correct.

18 Q. They have different effects?

19 A. Right.

20 Q. They have different harms?

21 A. Correct.

22 Q. So as a scientist, if you yourself set out to study harms,
23 you would be more interested in narrowly examining the
24 psychopharmacological effects of a drug than you would be to
25 the more simplistic task of saying, which of these two

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0C7UMCC5 Hanson - cross

1 substances is more harmful?

2 A. Right.

3 Q. Let's turn to neurotoxicity and its meaning and relevance.

4 Am I correct that since 2001, you and your colleagues
5 in this field are better technologically equipped to study
6 neurotoxicity?

7 A. In humans?

8 Q. Yes.

9 A. I would say that that's true to a certain extent. As I
10 mentioned, the tools we have are still somewhat limited and
11 they are ambiguous because we can only look so far into
12 underlying structure and function. But we are certainly
13 further along than we were in 2001.

14 Q. To take one example, perhaps the most important one for our
15 consideration, there have been advances in neuroimaging?

16 A. Correct.

17 Q. Since 2001?

18 A. Right.

19 Q. And those are reflected in the differences between the
20 McCann study and the Kish study, is that correct?

21 A. Yes. Dr. Kish, as he describes in his paper, he is more
22 selective than had been before.

23 Q. So it is fair to say simply that the techniques are more
24 developed and neuroimaging tells us more and better than it did
25 before?

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0C7UMCC5 Hanson - cross

- 1 A. It gives more precision than what we had before.
2 Q. As a result, more information and probably more accurate
3 information?
4 A. True.
5 Q. Staying with neurotoxicity and its definition, you describe
6 neurotoxicity as compromising normal function?
7 A. Correct.
8 Q. When a person's serotonin is decreased, you would say that
9 their normal function is compromised, correct?
10 A. Correct.
11 Q. That is the normal function of serotonin?
12 A. Of serotonin and anything that serotonin is influencing, so
13 you have a cascade of effects.
14 Q. When you talk about compromise and function there, you are
15 talking about brain change as opposed to functional impairment
16 in behavior?
17 A. But they are connected.
18 Q. There may be a correlation, but when you use that term,
19 that is, neurotoxicity and the depletion of serotonin, what you
20 are describing is a brain change?
21 A. But I would say, being a neurobiology type, I would say
22 that any behavior reflects neurochemistry, so you have changes
23 in neurochemistry. There are going to be changes in behavior
24 that will eventually be expressed. Whether you use the correct
25 test to pull that behavioral change out is always an issue of

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0C7UMCC5 Hanson - cross

1 discussion, but that's going to be the link. If you change
2 chemistry, eventually down the road you are going to impact
3 behavior in one way or another.

4 Q. But not all brain changes, for example, serotonin
5 depletion, have a direct correlation to functional impairment
6 in a person's behavior?

7 A. I think that they probably do if you were able to do the
8 right kinds of tests.

9 Q. Part of what we have been talking about here is whether or
10 not the field has done those kinds of tests?

11 A. And we may not be there. Our testing may be very crude,
12 and we still may not be asking all of the right questions. And
13 that's another piece that has changed a little bit from 2001 to
14 now is that the way we are asking the questions is changing a
15 little bit, but we are still getting the same answers, that is,
16 they are equivocal answers.

17 We are seeing changes sometimes and sometimes we are
18 not seeing the changes.

19 Q. In discussing neurotoxicity or the compromise of normal
20 function, there is a difference between acute compromise, that
21 is, immediate time-sensitive compromise and chronic compromise
22 or long-term compromise, correct?

23 A. Correct.

24 Q. You would draw that distinction and you can draw that
25 distinction in studies and tell pretty clearly what the

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0C7UMCC5 Hanson - cross

1 researchers have looked at, acute or chronic?

2 A. I would say that your point is correct, but there is a
3 continuum. There is a point where acute becomes chronic and
4 chronic becomes permanent. And it is not always easy to draw a
5 line and say, OK, you are done with the acute stuff. Now we
6 will look at the chronic stuff, because sometimes they just
7 melt into each other.

8 Q. But in evaluating a study, it is important to know and ask
9 questions about that study, when the evaluation took place in
10 relation to ingestion of the drug?

11 A. Correct.

12 Q. How much time has passed?

13 A. Yes.

14 Q. What other factors are involved?

15 A. Depending on the questions you are asking, but yes.

16 Q. All disruption in serotonin production is not necessarily
17 chronic, correct?

18 A. I think that that would be true.

19 Q. There is no disagreement that MDMA has the potential to
20 cause neurotoxicity, that is, compromise of normal function in
21 its acute status, that it has the potential to cause immediate
22 compromise, say, of serotonin levels?

23 A. Right.

24 Q. That is an area of agreement?

25 A. Yes. I would hope so, yes.

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0C7UMCC5 Hanson - cross

1 Q. But I took from your testimony that there is not an
2 agreement with respect to chronic compromise of normal
3 function?

4 A. Right. And if there is chronic compromise in the system,
5 what does that mean functionally, so it is a related but
6 different question.

7 Q. And that is a lot of what we have been talking about here
8 today?

9 A. Correct.

10 Q. I am trying to narrow down the area of disagreement.

11 A. Correct.

12 Q. And what I understand from you is, there's pretty good
13 agreement that there is acute disruption of normal function?

14 A. Right.

15 Q. There is not agreement that there's chronic disruption of
16 normal function?

17 A. I think that most people would say that there is the
18 potential for chronic disruption, but maybe the discussion is
19 how relevant is that potential to the real life, real world
20 situation.

21 Q. This distinction that we have just been discussing, acute
22 versus chronic, that was not a distinction that the commission
23 focused on in 2001, was it?

24 A. They didn't say it explicitly, but they implied it, that
25 is, they did talk about the immediate effects on cardiovascular

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0C7UMCC5 Hanson - cross

- 1 systems on emergencies and that sort of stuff. So that would
2 be acute toxicity. And they talked about more persistent
3 effects and that would be chronic toxicity. So they didn't use
4 that terminology, but I think they referred to the principles.
5 Q. In their summary of harms, they didn't make specific
6 reference to chronic impact?
7 A. I don't remember the exact enumerated things that they
8 included in their summary of harms, so I cannot say whether
9 they referred to chronic or acute.
10 Q. Let me refresh your recollection in a moment.
11 A. OK.
12 Q. Let's move back to our discussion of neuroimaging and the
13 effect of advances in the field.
14 A. OK.
15 Q. You identified the distinction between the McCann and Kish
16 neuroimaging studies, correct --
17 A. Right.
18 Q. -- and particularly the ways in which the Kish study
19 benefitted from those advances?
20 A. Right.
21 Q. Dr. McCann's study concluded and the commission relied on
22 that there were chronic effects, chronic problems with SERT
23 binding based on neuroimaging?
24 A. Right.
25 Q. Yet the Kish study concluded -- did not come to that

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1 conclusion?

2 A. Well, the studies were designed differently and the
3 subjects were different in terms of their Ecstasy experience.

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5 (Continued on next page)

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1 BY MR. RORTY:

2 Q. Let me refer you to one quote from there.

3 A. This is the Kish study.

4 Q. Yes. We did not find a global massive reduction of brain
5 SERT finding as reported in the first SERT imaging studies of
6 Ecstasy users. Then there is a citation to McCann.

7 A. Correct.

8 Q. So Kish did come to a different conclusion than McCann
9 although the studies may have had some differences in
10 methodology, Kish felt it was important to relate back and to
11 refer to McCann?

12 A. He does equivocate saying there is a distinction between
13 the intensity of use of subjects in the McCann versus ours and
14 he saw some tendency, I think he mentions that one or two of
15 his more intense users, they did appear to have some SERT
16 changes in the caudate or in the striatum. So I think he
17 distinguished the differences between his study and the McCann
18 study.

19 Q. He actually illustrates another important point I want to
20 ask you about. I took from your testimony that with respect to
21 chronic damage there is a significant difference between low to
22 moderate users and heavy users?

23 A. Correct.

24 Q. Am I correct that that awareness, that distinction between
25 low to moderate users and heavy users has been refined since

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1 2001?

2 A. Maybe refined but the basic principles have not changed.
3 We have known that for a long time. In fact, one of the
4 interesting things with the Kish study, I know Dr. Kish very
5 well, we have collaborated on a couple of studies in fact. He
6 called me about this study when they had completed it and he
7 asked me about the interpretation of the data. And he says,
8 so, does this go against what you guys have seen in the animal
9 studies. I said no, it's exactly what we have seen in the
10 animal studies, and that is the hippocampus and the cortical
11 structures are more sensitive to lower doses of MDMA than is
12 the caudate and the striatum.

13 so what I think he's got, he is looking at this lower
14 dose effect that those systems are sensitive to it, whereas the
15 caudate effects are not showing up and they don't show up until
16 you increase the doses

17 Q. The lower dose effect relates to what we understand to be
18 average recreational use in human beings?

19 A. Right. It would be more consistent with a typical
20 recreational Ecstasy user.

21 Q. You say we have known this for a long time. To a layperson
22 we have called this by a lot of names, but even to a layperson,
23 a person takes a small amount of drugs, they expect less harm,
24 a person takes a lots of drugs, they expect more harm?

25 A. That's pharmacology. Ecstasy does not violate the basic

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1 principles of pharmacology.

2 Q. Yet the commission's study, the 2001 report, did not itself
3 distinguish between low to moderate users and heavy users, did
4 it?

5 A. Well, I think what the commission was doing, unbeknownst to
6 themselves, was they were actually talking about what we call
7 benefit risk in the pharmacology world, and in this case the
8 benefit would be defined by the recreational users. They get
9 some recreational benefit from it, and how high do you have to
10 push the dose before you start to get some serious
11 consequences. And we do that whether the drug has been
12 FDA-approved or it has not been, it really doesn't matter to
13 the drug. But if there is a wide range, if there is a big
14 difference between the desired effect and the undesired effect,
15 then we consider it a good drug; if there is not much of a
16 range, then it's a bad drug and it gets us into trouble.

17 Q. Like cocaine?

18 A. Like cocaine and like Ecstasy, because Ecstasy, the drug
19 range already with recreational changes, we are sighing from
20 the Kish paper that you are getting some SERT changes in pretty
21 critical brain systems, in hippocampus and in cortical regions,
22 and my guess is if, I can't remember the explicit doses that
23 his high dose users were using, but if you get up to the 5
24 milligrams, this is certainly what we see in animals, we start
25 to see some of the SERT changes in the caudate. All you have

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0C74MCC6

Hanson - cross

1 to do is double or triple the dose and the effect is starting
2 expand and starting to hit other serotonin systems. That would
3 be a concern if it were a prescription drug and certainly a
4 concern in a recreational drug.

5 Q. In usage rates by heavy users at significantly greater use
6 rates than the average recreational user?

7 A. I think that's probably true.

8 Q. To highlight that, another quote from Kish: Nevertheless,
9 most Ecstasy users have few cognitive complaints after the
10 acute effects and the drug withdrawal phase has passed and user
11 values generally fell within the normal control range?

12 A. I would say that's true; most of them once they get to that
13 acute toxicity stage, then you probably don't hear a lot of
14 discussion about it.

15 Q. Because we have now established a distinction, the impact
16 of dosage rates between low to moderate users and heavy users,
17 that moves us to a discussion of dosage. I am going to ask you
18 some questions about your own work and dosage rates. Your own
19 experiments have been entirely in animal systems?

20 A. That's true.

21 Q. You have not done an MDMA animal study since 2005?

22 A. Actually we have; we have not published. We always throw
23 in MDMA for comparison to other drugs because it has a unique
24 pharmacology profile that helps to elucidate mechanisms, but we
25 have not published.

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1 Q. Your pre 2005 research on MDMA were animal studies?

2 A. Correct.

3 Q. Am I correct that you usually use 10 milligrams per
4 kilogram or more of MDMA as your dosage unit in your previous
5 animal studies?

6 A. That's correct, although as I have said we will find
7 effects with 5, but when you are doing research like that, you
8 want a very robust effect. So you kind of find a dose that's
9 not going to be lethal. 10 never kills any animals and doesn't
10 cause seizures. The animals do quite nicely. They survive 10
11 without any problems. We get changes are like 50, 60, 70
12 percent changes. We can start to tease mechanisms apart.

13 Q. You increase the dosage to achieve a more robust effect?

14 A. Correct. In effect, we can see at half that dose, but you
15 are talking more like 20 and 30 percent changes versus 50 to 70
16 percent.

17 Q. If you were to undertake animal studies now would you use
18 the same dosage?

19 A. Yes. Let me equivocate a little bit. One thing that has
20 not been done, and Michael Baumann is one of the nice papers
21 that is starting to look at this. That is, to look at the 1 to
22 2 milligram per kilogram range, and Dr. Baumann says that he's
23 done this exercise that tries to equate doses and he finds
24 that the doses equate pretty well across species. So 1 to 2
25 milligrams per kilograms in a rat give effects that are

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1 probably fairly similar to 1 to 2 milligrams per kilogram in
2 humans.

3 He doesn't see the serotonin transport decreases. I
4 have talked with Michael ad nauseam about this issue. But what
5 he does see, he does see some functional changes, and he says,
6 well, since we don't see serotonin decreases, serotonin
7 transport decreases, we don't call that neurotoxicity. My
8 response is, but, Dr. Baumann, if you are getting persistent
9 functional changes, then how can you not call it toxicity when
10 the definition of toxicity is you interfere with normal
11 functioning. So he went, well, it just depends on how you
12 define the word.

13 Q. You said a number of things about Dr. Baumann's work. It
14 sounds like you understand and to some degree accept his
15 interest in the effect of a lower dose?

16 A. Correct.

17 Q. So that 1 to 2 milligrams per kilogram is a perfectly
18 appropriate acceptable way to conduct animal studies?

19 A. Absolutely. The question he is asking is what would you
20 routinely see in a person who is this recreational user and
21 only uses one tablet every time they go to a rave once every
22 month. That's the kind of question he is trying to address.

23 Q. Let's make sure we are talking about the same paper. There
24 is a 2007 study of Baumann, Wang and Rothman?

25 A. Right.

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1 Q. MDMA neurotoxicity in rats: a reappraisal of past and
2 present findings, Baumann et al. 2007. That's the paper we
3 have been discussing?

4 A. It is.

5 Q. I take from the answer you just gave that you think that is
6 a useful tool in measuring neurotoxicity in animals then
7 translating those findings to an average recreational human
8 user?

9 A. Yes.

10 Q. To the extent you would be interested in increasing dosage,
11 you would be measuring the potential harms to heavy users?

12 A. Heavy users or people who are very sensitive to the drug.
13 That's always going to be part of this discussion. We are
14 talking about average responses and there are always going to
15 be those folks on either side of the bell curve who are
16 extraordinarily sensitive to the drug. So whether they don't
17 metabolize the drug very well or their brain serotonin systems
18 are exquisitely sensitive to a drug like this, you are always
19 going to have those folks in there as well.

20 Q. That sensitivity is different from confounds such as mental
21 health?

22 A. No, it could be the same thing. It could be that they have
23 got a serotonin system that's not functioning normally anyway
24 and that's expressing and they have a tendency towards
25 depression. Maybe they are not really depressed so long as

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- 1 everything stays in a normal routine, healthy way, and now they
2 put a drug on top of it that further compromises that system
3 and it pushes it down. That sensitivity sets them up both for
4 problems with the drug as well as problems with the mental
5 health issue.
- 6 Q. There are a variety of sensitivities that can affect the
7 way a person is going to respond to MDMA?
- 8 A. Exactly.
- 9 Q. Some of those are mental health related, some of those are
10 iconoclastic individuals brain chemistries different from
11 mental health diagnoses?
- 12 A. Right or could be associated in one way or another.
- 13 Q. I would like to move to your own summary report. Did you
14 yourself draft that report?
- 15 A. I did.
- 16 Q. I take it no changes; you stand by its contents?
- 17 A. Yes.
- 18 Q. In that summary you talked about MDMA's association with
19 serious toxicities of the liver. In its acute phase, when
20 someone takes MDMA, you would expect to see a change in liver
21 enzymes, is that correct?
- 22 A. Yes, I would.
- 23 Q. That's because the function of the liver is to process --
24 that's what it does.
- 25 A. This family or group of drugs are somewhat notorious for

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1 changing the hepatic enzymes that are responsible for
2 metabolism.

3 Q. Distinguish acute versus chronic effects; when you speak of
4 serious toxicities of the liver, you just described the fact
5 there are significant acute effects to the liver during a
6 period of use?

7 A. Right.

8 Q. But those pass through, the liver regenerates, correct?

9 A. Recovers, yes.

10 Q. Recovers from that acute phase?

11 A. Correct.

12 Q. When you say serious toxicities, are you speaking of the
13 acute phase?

14 A. Yes.

15 Q. You talked about cardiovascular harm as well?

16 A. Right.

17 Q. When Mr. Chung was inquiring you spoke of a number of
18 cardiovascular harms, elevated heart rate, increased blood
19 pressure, a number of other things?

20 A. Right.

21 Q. We are again speaking of the acute phase with respect to
22 those cardiovascular effects?

23 A. Yes, typically unless you have a heart attack; then you are
24 going to have chronic but yes.

25 Q. You also say in your summary MDMA causes hyperthermia much

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1 like amphetamines. Just to clarify, hyperthermia generally
2 means elevated body temperature?

3 A. Yes.

4 Q. MDMA causes hyperthermia in its acute period just after
5 ingestion?

6 A. Right. As I explained, it interferes with thermal
7 regulation and so the environment plus that is what causes the
8 hyperthermia.

9 Q. That has not been shown to have that chronic effect?

10 A. No. Once the drug is gone, that effect is gone.

11 Q. Your next point in the summary was that heavy MDMA use has
12 been associated with neurocognitive impairment. We have
13 already discussed that. That refers to the neurotoxicity issue
14 that you and I have just been discussing and that you discussed
15 with Mr. Chung?

16 A. Correct.

17 Q. I don't know whether you can put a number on this but when
18 you say heavy MDMA use in your summary, say what you meant by
19 that in terms of both dosage and frequency, separating them, if
20 you will.

21 A. I think that's a critical point. With MDMA use compared to
22 the animal models, we rarely do repetitive exposure with animal
23 models, again for logistic, practical reasons. But there may
24 well be an accumulative phenomenon that's going on with MDMA.
25 That has not been looked at. This is a big question we need to

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1 address with future research. So if you have somebody that's
2 exposed let's say in a 24-hour period to 2 or 3 tablets of
3 Ecstasy, they are getting about 300 milligrams per kilogram of
4 the Ecstasy in the 24-hour period.

5 Q. You said 300 milligrams, 2 to 3 tablets. I know you were
6 present when Mr. Parrott testified; he characterized the
7 average tablet dose at 70?

8 A. 70 in England.

9 Q. Is there a different figure that's been demonstrated in the
10 United States?

11 A. Yes. It varies. There are some places have been up as
12 high as 120 milligrams, so it does vary on batches. I was also
13 talking to Dr. Parrott. He said now they found some batches
14 that don't have any Ecstasy in it but they are being sold as
15 Ecstasy. That's one of the problems with this world. You
16 don't always know how much of the drug you are going to get or
17 if your going to get another drug in combination with the
18 Ecstasy, so that confounds our interpretation of the human data
19 when we see something or we don't see something, is it because
20 the drug was there or it wasn't there or there was another drug
21 there. So that's always an issue.

22 Q. I interrupted you to clarify. Continue.

23 A. The point I am trying to make is that if this person does
24 the same routine every week for a year, even though they are
25 not looking at the 5 to 10 milligrams per kilogram that we look

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1 at in our intense exposure but the accumulative exposure to the
2 drug is much higher over the course of a year, what does that
3 mean. In all honesty we don't know what that means because our
4 animal research has not looked at this in specific, but almost
5 all of our human research has that confound and it doesn't know
6 what to do with it.

7 Q. The frequency you just described would be associated with
8 heavy use and it's distinct from the moderate, average
9 recreational user, correct?

10 A. I would say that the average user probably wouldn't be
11 using it on a weekly basis. They certainly could be using
12 those doses on a monthly basis or every other month kind of
13 basis. Someone doing it weekly you would put into a category
14 of more intense use.

15 Q. Staying with this moderate user versus heavy user
16 distinction, are you aware of data in the United States that
17 attempts to categorize the percentages of users who would
18 qualify as heavy users within the definition you just
19 described?

20 A. I have looked for that and if you know a source let me
21 know. I have not been able to find that although Great Britain
22 and Australia who have big Ecstasy problems, they have looked
23 at that. For example, in Great Britain there is anywhere from
24 1 to 3 percent of the people in their treatment. So this is
25 treatment for every drug abuse issue, alcohol, cocaine, what

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1 have you. About 1 to 3 percent are being treated for Ecstasy
2 problems. So that would suggest kind of a number, you would
3 have to do the math in terms of how many are using what have
4 you.

5 Other studies have suggested that, like the Bruno
6 study, there is this 20 percent, those users who are exhibiting
7 dependence, significant dependence, and does that mean they are
8 all addicted or just physically dependent, trying to avoid
9 withdrawal. It doesn't equivocate that very well. It does say
10 there is a significant proportion of these people who go on to
11 become moderate to heavy users.

12 Q. Back to where you started with that point, if the
13 percentage of people who report, who sought treatment for
14 MDMA-related issues would be an indicator of the percentage of
15 users who are categorized as heavy users within the criteria we
16 have just described?

17 A. Correct, if you can do the math. What I said is 1 to 3
18 percent of everybody that's in treatment is there because of
19 MDMA, so you have to figure out what's the number of Ecstasy
20 users and then calculate how many are actually in treatment,
21 then do the math.

22 Q. The answer wouldn't be 1 to 3 percent; it would be
23 something different based on the total number of MDMA users?

24 A. Exactly. One of the things Kish mentions in his papers, he
25 says about 40 percent of those people, those subjects that were

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1 in their study described the process of tolerance and dose
2 escalation. So we know that Ecstasy does cause tolerance.
3 That's a fairly common phenomenon. People start to escalate.

4 Here again, we don't have a lot of research as to what
5 that means. Once tolerance occurs, does that mean the body or
6 the brain has changed in some basic neurobiological ways, is
7 that a good thing, a bad thing, and they start to escalate
8 their doses. Are they sensitized. Sensitization is a
9 phenomenon with psychostimulants.

10 We see it with cocaine and methamphetamine which means
11 that you start off with lower doses but as you use it over a
12 period of time, you find that the system becomes more and more
13 sensitive to the drug and not less and less sensitive, so we
14 don't know what sensitization looks like with Ecstasy. No one
15 has really looked at that very carefully.

16 Q. We will talk more about that in relation to dependence. I
17 am moving through your summary. We will get back to your
18 points. The next point you make in your summary relates to
19 fatalities. Let's talk about that. You say deaths from MDMA
20 abuse are comparable to those linked to methamphetamine and
21 cocaine abuse. What do you mean by comparable; do you mean the
22 fatality rate, that MDMA causes as many deaths as cocaine?

23 A. This again comes from some of the Great Britain studies and
24 Australia studies. These investigators have concluded, one of
25 the studies looks at, it's a fairly complicated formula, they

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1 look at availability, they look at seizures, look at things
2 that measure how much of the drug is being used and they
3 concluded that if had a fatality potential similar to cocaine
4 and amphetamine.

5 Q. Can you name the study you are describing.

6 A. It's Schifano.

7 Q. There is a Schifano study; I want to make sure we are
8 talking about the same one.

9 A. There is another called King study that I think I indicated
10 that they also do this comparison between methamphetamine and
11 then a third one is the Kaye study and they are looking at
12 Australia and trying to equate, and they conclude that the
13 toxicity, the lethal toxicity is fairly similar between all of
14 them.

15 Q. Let's talk about that in context of the Schifano study.
16 The Schifano study looked at, distinguished between related
17 death, cocaine or MDMA related deaths, and causal deaths, did
18 it not? It drew a distinction a death which is related to
19 ingestion of the drug and caused by the drug?

20 A. Correct.

21 Q. That distinction was that a death was related to the drug
22 if the drug was present in the system of the person who died
23 when they died?

24 A. Correct.

25 Q. Or when examined shortly thereafter?

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- 1 A. Right.
- 2 Q. By that logic a person who was under the influence of MDMA
- 3 and stepped off the curb and was hit by a drunk driver would be
- 4 called an MDMA-related death?
- 5 A. Correct.
- 6 Q. Not caused by MDMA but related to MDMA?
- 7 A. Yes, that's fine.
- 8 Q. They drew a distinction and looked more carefully at those
- 9 cases where coroners have listed the drug as the cause of death
- 10 and teased out those numbers in term of fatalities?
- 11 A. Yes.
- 12 Q. With respect to MDMA, do you recall figures in Schifano?
- 13 A. I don't recall breaking them down to that degree but it
- 14 seems like they start off with 800 versus 600 then they start
- 15 to break them down into their packages.
- 16 Q. With MDMA it would help you to recall that there were 104
- 17 MDMA-caused deaths in 10 years, approximately 10 per year?
- 18 A. That would be fine.
- 19 Q. Is it your recollection that cocaine-caused deaths were
- 20 similar?
- 21 A. No, they would have been higher than that.
- 22 Q. When we compare fatalities, in causation, not relationship
- 23 but causation, MDMA is less likely to cause fatalities than
- 24 cocaine?
- 25 A. Yes. What does the drug itself do and you would also keep

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1 in mind that the doses these people are exposing themselves are
2 going to be much different. The cocaine person is going to be
3 on a cocaine binge sometimes so you are going to have a much
4 higher dose.

5 Q. That wasn't known in the study?

6 A. No.

7 Q. That variable was not accounted for in that study?

8 A. It was not.

9 Q. So the conclusion of that study is that cocaine causes more
10 fatalities than MDMA?

11 A. Correct.

12 Q. You mentioned two other studies; they used different
13 variables?

14 A. They did.

15 Q. The bottom line of those studies is the same, that is, that
16 cocaine causes more fatalities than MDMA?

17 A. Correct. They are comparing with amphetamines as well. As
18 I recall, the King study makes a statement they are kind of
19 equivalent in terms of their mortality potential.

20 Q. Let's go back to an area we were discussing before, that's
21 dependence. We have touched on that in a number of ways; we
22 have all touched on it.

23 A. Right.

24 Q. Would you agree with the statement MDMA is not addictive
25 but has addictive potential?

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1 A. Well, those almost sound like they are mutually exclusive.
2 I would say that under normal recreational uses, the likelihood
3 of addiction is fairly low but it does have addiction potential
4 with escalating doses and all those qualifiers.

5 Q. Those would be for the hard to quantify but recognized
6 heavy user population we discussed?

7 A. Yes. Almost by definition, if you are addicted you are
8 going to be a heavy user because you have compulsive behavior
9 and you need to use the drug.

10 Q. I take it from that, a person who used with level frequency
11 over time once to twice a month but continued to use at that
12 rate would not qualify as addicted?

13 A. They wouldn't satisfy that compulsive behavior definition
14 of addiction, that's correct.

15 Q. You are making reference I think to the DSM criteria for
16 dependence?

17 A. World Health Organization definition of addiction, right.

18 Q. One of those factors is compulsive?

19 A. Correct. The distinguishing feature there is that the
20 behavior is so overwhelming that you want the drug, you need
21 the drug despite the fact that it's having some fairly negative
22 consequences in your life.

23 Q. When we talk about heavy use that invokes this addiction
24 potential in MDMA, again, we are very limited in our data as to
25 what percentage of users we are talking about?

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- 1 A. Correct.
- 2 Q. That takes us back to the same question we talked about
- 3 earlier, number of people who report for treatment, number of
- 4 people who are admitted to emergency rooms, that kind of data
- 5 would be useful in trying to understand.
- 6 A. It would, although the emergency room data, so many other
- 7 things are going on there, a lot of times people who show up in
- 8 emergency rooms are people who may have their first exposure to
- 9 this drug and they don't know what they were doing and took too
- 10 much, whatever.
- 11 Q. Dr. Parrott said that unlike cocaine users even heavy users
- 12 generally decline in their use of MDMA; would you agree with
- 13 that?
- 14 A. I have certainly heard that that's the case for a lot of
- 15 those users.
- 16 Q. Although there is escalating use for some period, we
- 17 generally see a decline?
- 18 A. Right.
- 19 Q. That's not true for cocaine?
- 20 A. That's correct.
- 21 Q. Or heroin?
- 22 A. That's correct.
- 23 Q. It's a different kind of addiction. Cocaine users will use
- 24 and use until the money is gone and the life has run out?
- 25 A. That's correct. It's sort of a 2-phase, and that reflects

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1 the psychedelic, hallucinogenic serotonin piece, and the
2 addicting, euphoric, energizing dopamine piece and this
3 interaction between those two systems.

4 Q. You talked about the differences between the drugs and the
5 stimulant and hallucinogen properties. I am going to come back
6 to the 2001 sentencing commission report characterized as one
7 of the concerns, one of the harms of MDMA is its both stimulant
8 and hallucinogenic properties. Do you recall that?

9 A. Yes, I do.

10 Q. We were talking about apples and oranges and that
11 comparison between cocaine and MDMA. The same question that
12 was asked of Dr. Parrott, that just because something has two
13 properties instead of one, that is, both a stimulant and a
14 hallucinogen, that doesn't make it doubly dangerous, does it?

15 A. In principle I would say that's true, but in regard to this
16 drug, that's the basis for its appeal to the young population.
17 They love the hallucinogenic, psychedelic enhancing of sensory
18 elements. That's why they go to the rave. The rave is filled
19 with all sorts of sensory things going on. They love the
20 stimulus piece. It gives them the energy, it sort of
21 reinforces.

22 You can kind of imagine that combination would be very
23 fascinating to a young person. It's a hug drug. It's got this
24 entactogenic property that they really like. It enhances love,
25 at least as they define love. But on top of that you are

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1 stimulating that mesolimbic dopamine pathway so you are getting
2 the reward. This interaction is very appealing. That's why
3 it's particularly dangerous, particularly problematic for that
4 group of people.

5 Q. You just made an interesting leap. All the reasons you
6 just described are reasons it's more attractive to a user,
7 correct?

8 A. Particularly youth.

9 Q. You described what you define to be more attractive but you
10 leapt to more dangerous. I take that leap to simply be if it's
11 attractive to youth, it is by definition more dangerous?

12 A. We know that the youth population is particularly
13 vulnerable to effects of drugs. We know they are more
14 vulnerable to alcohol, they are more vulnerable to smoking. I
15 can't think of a drug, there is probably some exception to that
16 rule, the reason is that in adolescents and even in adults,
17 young adult stage, brain systems are still developing,
18 serotonin systems, dopamine sometimes.

19 All of these things are still coming together and if
20 you start to sprinkle neurochemistry on top of that, the data
21 suggest, even marijuana, use of marijuana during adolescence or
22 during the developing brain will change the way that brain
23 develops and what it looks like when they become an adult.

24 Q. What you have just said is essentially true for all
25 dangerous drugs?

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Hanson - cross

- 1 A. It is. So if you have a drug that is particularly
2 appealing to that population, then in a way you are sort of
3 lighting a match to the fire. You are bringing those two
4 things together and increasing the likelihood that you can
5 cause problems for this person as their brain develops.
6 Q. The region you just entered into is far more cultural and
7 sociological than psychopharmacological, correct, that is,
8 psychopharmacologically speaking, the combination of stimulant
9 plus hallucinogen properties is not a double in effect?
10 A. Well it's a more intriguing effect to these kids; as you
11 know, adolescents are all into intrigue and new experiences.
12 So it gives them this unique combination of pharmacology that
13 is very appealing to them.
14 Q. You just made a leap into behavior and culture again rather
15 than rooting your answer in psychopharmacology.
16 A. I am not sure you can separate these things quite honestly.
17 Maybe that's the neurobiology in me. I sort of see the world
18 through a neurobiological window. It's hard for me to make the
19 distinction because I think that they connect with each other.
20 Q. We have touched on this before and you mentioned the
21 significance of emergency room data. You are aware that the
22 commission looked at and mentioned emergency room admission in
23 its consideration of harm, correct?
24 A. Right.
25 Q. And you would agree that emergency room admissions are an

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0C74MCC6 Hanson - cross

1 appropriate indicator of harm?

2 A. Correct.

3 Q. You are aware of the national survey of drug use and
4 health?

5 A. Yes.

6 Q. And that is an ongoing study and they have had a number of
7 reports that track usage of particular drugs?

8 A. Right.

9 Q. Are you aware of the Dawn data?

10 A. I am.

11 Q. With respect to emergency room admission?

12 A. Yes.

13 Q. According to this data approximately 6 million people use
14 cocaine resulting in approximately 550,000 emergency room
15 admissions?

16 A. Right.

17 Q. Equating to about 9.3 percent of users admitted to
18 emergency rooms?

19 A. Yes.

20 Q. With MDMA approximately 2 million users with 15,000
21 admitted to the emergency room?

22 A. Right.

23 Q. That's equating to .7 percent admission rate among users?

24 A. Right.

25 Q. So by that metric certainly we would say that MDMA is less

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0C74MCC6 Hanson - cross

1 harmful than cocaine?

2 A. Yes, numerically there is certainly that difference. If
3 you look at the data, you will also see that those that end up
4 in emergency rooms because of Ecstasy use tend to be
5 significantly younger than those who end up in emergency rooms
6 because of cocaine and they also tend to be healthier which
7 goes to the issue of there is this unique young population
8 that's particularly attracted to this drug and they get into
9 trouble with it sometimes.

10 Q. A significantly smaller percentage of them than cocaine
11 users?

12 A. If you are just going by numbers, yes.

13 Q. The methamphetamine portion of users admitted to emergency
14 rooms is also significantly higher than MDMA?

15 A. I would expect it to be.

16 Q. I don't believe you were asked about systematic reviews and
17 their role in the research. Are you familiar with that term?

18 A. Like meta-analysis?

19 Q. Exactly.

20 A. Yes.

21 Q. Properly controlled are meta-analyses a useful tool?

22 A. Absolutely. I think they give you a lay of the land.

23 Q. Is the Rodgers 2007 study a good example of a well-done
24 systematic review?

25 A. I am not aware, I know the study but I did not examine the

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0C74MCC6 Hanson - cross

1 details in it. So I would leave that to others, Dr. Parrott
2 and others.

3 Q. In contrast to a systematic review there is another kind of
4 study called a narrative review?

5 A. Yes.

6 Q. Am I correct that narrative reviews, the value of narrative
7 reviews is dependent on the selection criteria used by the
8 reviewer?

9 A. Absolutely.

10 Q. Also by the extent to which the reviewer includes data
11 which contradicts or calls into question their conclusions?

12 A. Correct.

13 Q. So a well-done narrative review would list not only those
14 studies which ultimately support the conclusion of the reviewer
15 but also any studies which reach opposite conclusions and then
16 would compare the two?

17 A. Right.

18 Q. We talked about confounding factors. You made an important
19 point with Mr. Chung that polydrug use is a confounding factor?

20 A. Correct.

21 Q. Most Ecstasy users are polydrug users?

22 A. Correct.

23 Q. You are interested in studying the co-effects of MDMA with
24 other drugs?

25 A. Yes.

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Hanson - cross

1 Q. You think that is an important question for research?

2 A. Yes.

3 Q. However, we talked earlier about ways in which the
4 commission and this court are as nonscientists, as lawyers and
5 judges attempting to assess harms for purposes of criminal
6 penalties, attempting to separate out the isolated harms of
7 MDMA. Would you agree these are two different tasks?

8 A. They certainly are related tasks. From a scientific
9 perspective it's difficult to understand interaction if you
10 don't understand what drugs do by themselves. So the isolated
11 approach is always helpful in terms of interpreting the more
12 practical interacting issues although sometimes it can lead you
13 down a road that you don't want to go and tell you something
14 that is not very useful.

15 Q. What I take from all of our discussion about all of the
16 years of MDMA study is that because of the prevalence of
17 polydrug use and the ethical and legal and other limitations on
18 isolated MDMA studies, the field is fairly new in terms of
19 psychopharmacologists absolutely isolating the effects of MDMA
20 alone, correct?

21 A. In humans?

22 Q. In humans, yes.

23 A. And the reason is, boy, it's really hard to find these
24 people.

25 Q. To the extent that studies are able to isolate monodrug,

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Hanson - cross

1 MDMA-only users and compare them with nondrug users, those are
2 pretty useful in helping us answer the question about the
3 isolated impact of MDMA. Am I correct?

4 A. But there are some landmines there and that is that in
5 finding a population that only uses Ecstasy, have you also
6 found a population that has other factors that you may not be
7 aware of that in and of themselves cause the behavior of only
8 using Ecstasy but does not generalize to the big population
9 that are polydrug users. See what I am saying?

10 Q. I do, but that would be in terms of psychopharmacological
11 analysis, what is the effect on the brain of this drug?

12 A. Let me give you an example. This population does not use
13 any other drugs. That tells you something about this youth,
14 this group of adolescents, young adults. It tells you
15 something about their environment is going to be different than
16 these other people.

17 It tells you probably something about their attitude
18 towards risk, what does risk mean. We know that risk, high
19 risk behavior is very predictive of tendency towards addiction.
20 It may tell you something about what's the likelihood that this
21 group would ever get addicted to this drug. It's probably very
22 small because they don't have that tendency. And it tells you
23 something about what's happening in the community, would the
24 community tolerate heavy use of this drug.

25 There are all these factors that have gone into

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Hanson - cross

1 isolating a very small group. If you come and you do a study
2 on that very small group and these other factors may be
3 critical issues for determining the outcome you want to
4 measure, you don't see much outcome in these folks because they
5 don't have those factors.

6 Q. Understood. Another way of saying that is in the rest of
7 the world, in the analysis of polydrug users with many of the
8 confounds that have complicated the research, you are better
9 able to test things like addiction potential in polydrug users
10 which is the more common effect?

11 A. And you are probably better able to detect or to measure
12 things such as toxicities, acute and long-term toxicities,
13 because some of the toxicities that MDMA or a drug might cause
14 have to do with how they interact with these other drugs or how
15 they interact with a body that's been affected by these other
16 drugs, and that's not going to be present.

17 It also may have to do with one of the ways they
18 design or find their subjects. They say they used one tablet,
19 or one MDMA tablet. Well, maybe these kids, because they are
20 kind of aversive to risk and they are concerned about what
21 might Ecstasy do to me. They go in very conservatively and
22 cautiously and they kind of nibble on the tablet or they don't
23 eat the whole tablet or they heard that heat can worsen the
24 likelihood of causing side effects with this so they are making
25 sure they are drinking lots of water so it won't cause a

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0C74MCC6 Hanson - cross

1 problem for them. Or we had discovered a while back that
2 Prozac protected against the damage caused by Ecstasy, so maybe
3 they took a Prozac from mom and dad's medicine cabinet.

4 I am just giving those as examples of their approach
5 to using Ecstasy might be very different than someone who is
6 very high-risk oriented and has lots of drugs and their
7 attitudes and strategies can be distinct.

8 Q. All the factors you just described about what might be
9 confounding elements in an MDMA-only user survey, that's not
10 based on your analysis of any particular study; that's a
11 hypothesis about what might occur in such a hypothetical
12 population?

13 A. That's correct, but it also gives me pause when I try to
14 interpret and extrapolate what I found in this population to
15 more global presentation.

16 Q. If your goal was to understand the pure and isolated
17 effects of MDMA, you would rather have a study with MDMA users
18 only than on polydrug users, correct?

19 A. So long as I put that caveat in there recognizing this may
20 be a very unique population so whatever happens, you've got to
21 be careful in terms of interpreting its significance.

22 MR. RORTY: Thank you very much.

23 No further questions.

24 THE COURT: Mr. Chung.

25 MR. CHUNG: No redirect.

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Hanson - cross

1 THE COURT: From your perspective, Dr. Hanson, as a
2 researcher, what is the best way empirically to try to measure
3 the harms from a particular drug?

4 THE WITNESS: I guess it depends on what harms you are
5 interested in. It's always hard to do the global analysis and
6 say let's just talk about harms and adverse effects. You also
7 almost have to focus in because if it's very global you miss
8 stuff. But if you can focus in and say let's talk about the
9 cardiovascular harms, how would this affect that, or how does
10 this affect your liver function. Those are relatively easy to
11 measure. We can hook you up to machines or take your blood and
12 analyze it and get a pretty good sense as to what's going on.

13 It becomes more difficult when you get into behavioral
14 analysis because that's so complex. A person could do one
15 thing under one setting and it looks perfectly normal but they
16 do the same thing in another setting and it looks pathologic or
17 it's problematic. How do you make that distinction. Did the
18 drug cause that. It looks like a normal behavior but the
19 problem isn't so much behavior but it's their interpretation of
20 the environment and deciding what's the appropriate behavior to
21 put into that setting.

22 So those things are very hard to analyze. And then we
23 have the longitudinal issues. I mentioned with methamphetamine
24 we have just now found out that meth-dependent people have a
25 five-fold increase in the likelihood of developing Parkinson's.

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Hanson - cross

1 This is something they started 20 years ago. How do I link
2 what they did 20 years ago with what's going to happen to them
3 down the road.

4 Those are some of the problems we wrestle with with
5 drugs luck Ecstasy that we know is really having a profound
6 effect on brain chemistry. We know that. Now it's having a
7 profound effect in the immediate future and there is a
8 discussion as how far does that go and what does that cascade
9 of events do. At the end of days you come to a person just
10 before they are buried and you say, how was life, and they tell
11 you, it was great, I enjoyed it, then you would say, OK, I
12 guess you didn't have any big problems with drugs

13 On the other hand if they say life was horrible, I had
14 all kinds of problems with my family, I couldn't keep a job,
15 then you would said, oh, it likes like maybe drugs caused a big
16 problem for you. So hard to do, don't know that's very
17 satisfying answer, but it gives you a sense of how difficult
18 the question is.

19 THE COURT: In your testimony today you have talked
20 about the particular attractiveness to young people of MDMA
21 because of the combination of both the stimulant and the
22 hallucinogen.

23 THE WITNESS: Right.

24 THE COURT: At the time of the Sentencing Commission
25 report to Congress, there was a wave of MDMA cases around the

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0C74MCC6 Hanson - cross

1 country. Over the last 10 years, what have you seen from your
2 vantage point in terms of the use of MDMA?

3 THE WITNESS: This is a drug that's very sensitive to
4 perceived risk and when that youthful population sees the drug
5 having potential of severe toxicity and problems, they tend to
6 move away from it. So it's interesting. You can argue whether
7 the data were completely accurate or whether we did the best
8 thing, but it's interesting that after that 2001 where we
9 really had a major epidemic, 9 percent of our youth were trying
10 and experimenting with this drug, it dropped. You get to 2005,
11 and it drops down to about 3 percent. That's big cut over a
12 period of 3 to 4 years. Now we are starting to see a
13 resurgence, not a dramatic resurgence, but we are back up to
14 about 4-1/2 percent, so we have come up from the bottom.

15 THE COURT: Do what do you attribute that?

16 THE WITNESS: Lloyd Johnston is the one who does
17 monitoring the future. This is a NIDA-sponsored survey. He
18 says that there is a good correlation between perceived risk of
19 the drug and the likelihood they would use it. So as they
20 analyzed their surveyed risk, they saw risk, perceived risk for
21 Ecstasy went up and use went down. Now they are seeing
22 perceived risk as going down and use is starting to come back
23 up. So, there is that connection and there are lots of factors
24 that contribute to perceived risk.

25 One of the factors is that the media is really

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Hanson - cross

1 covering this FDA-approved clinical trial of Ecstasy for PTSD.
2 I am not saying it's good and I am not saying it's bad.
3 Personally I have no problem and I wouldn't be surprised if
4 indeed it is of some value in treating PTSD. We use
5 methamphetamine to treat ADHD. We use some of these drugs of
6 abuse to treat. They have perfectly legitimate medical use.
7 It's when we are throwing it out and people are using
8 it on their own and they are being their own doctors or using
9 it recreationally, we have no control over that, you get into
10 trouble with it. Having said that, as you took to youth, I
11 teach a class at the University of Utah called common
12 medicines. We just talk about drugs. We talk about Ecstasy
13 and I get some feedback. I say what do you think about
14 Ecstasy, what's your attitude. They say it's not a very
15 harmful drug. And I say why do you say that. They say we just
16 read in the newspapers it's being used to treat PTSD. How
17 could it be helping these people who are struggling with PTSD
18 and be harmful.
19 That kind of attitude. I am not saying those kids
20 will go out and use it. It's certainly the perceived risk
21 issue that's happening. Again I am not saying that's bad or
22 that's good, I am saying that is a reality. It's attractive,
23 they go out and use it. The more they use it, the more people
24 you are going to have that will get into trouble with it.
25 That's just basic pharmacology.

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Hanson - cross

1 THE COURT: You say you have seen an uptick.

2 THE WITNESS: Correct.

3 THE COURT: Can you put a timeframe on that for me.

4 THE WITNESS: It hit bottom 2005, it kind of stayed
5 around there for 2005, 2006, and 2007 it started to climb, then
6 our latest data, we have not got the 2010 data yet, the 2009,
7 it's come up to about 4.5, 4.6 in high school seniors.

8 THE COURT: I reviewed with others the principal bases
9 on which the Sentencing Commission rested its report to
10 Congress. I would like to hear your comments on those three
11 observations from the report. I am reading from page 5 in
12 which the commission stated that it shows a greater penalty
13 structure for MDMA trafficking than for powder cocaine
14 trafficking because, 1, unlike MDMA, powder cocaine is not
15 neurotoxic. I will take these seriatim, if you would comment
16 on that.

17 THE WITNESS: Probably some of that came from my
18 testimony because we find that in the animal model and in
19 humans, we have gone back mostly have done postmortem studies
20 to try to analyze if it's disruptive to things such as
21 serotonin systems or dopamine systems, whatever, and we don't
22 see a lot of persistent neurotoxicity. It doesn't have that
23 pattern like the amphetamines and Ecstasy for serotonin. We
24 don't see the deficits.

25 In my laboratory we tried, we thought way back when
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Hanson - cross

1 that cocaine would probably look a lot like the amphetamines
2 and we didn't ever see persistence in toxicity to either the
3 dopamine or the serotonin system like we do with Ecstasy and
4 like what we do with methamphetamine. That's probably where
5 that statement came from. Based on that that's true. We don't
6 see that kind of persistent toxicity that you see with the
7 amphetamines.

8 (Continued on next page)

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1 THE COURT: The commission went on to note as a second
2 reason that powdered cocaine is not aggressively marketed to
3 youth in the same manner as MDMA.

4 THE WITNESS: That is true. It doesn't have the
5 appeal to the young people that MDMA does. And a lot of it is
6 this perceived risk issue, that they don't see MDMA as a risk
7 for them and so they are more inclined to do that.

8 Even kids in Salt Lake City are not going to use
9 cocaine, but they will MDMA. We know that that can be terribly
10 dangerous, so they are willing to go out and try it. So, yes,
11 we see it and, as a general rule, the population that is most
12 affected is going to be a younger population.

13 THE COURT: We heard testimony that there comes a time
14 generally in the use cycle of MDMA that people simply quit --

15 THE WITNESS: Right.

16 THE COURT: -- MDMA. Can you explain that to me
17 because it seems so different from other drugs like cocaine?

18 THE WITNESS: Some of this is just conjecture on my
19 part because it would be very interesting to go and get these
20 individuals who had used compulsively and then they just
21 stopped. If you could have a brain image of what their brain
22 image looked like before and what it looked like afterwards, I
23 wouldn't be surprised if there isn't maybe a pathological
24 explanation, that is, they could have used the drug in an
25 intense fashion for so long that it compromised systems, maybe

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1 systems that have to do with motivation, maybe systems that
2 have to do with interpretation, whatever. But now because
3 that's been compromised, they are no longer interested in the
4 drug per se. So it may not reflect a good thing. I mean, it
5 may reflect a good thing, I don't know. It may actually
6 reflect a pathology but just reflect that they finally figured
7 it out, they grew up and they moved on.

8 THE COURT: The third factor that the commission cites
9 is that powdered cocaine is only a stimulant, but MDMA acts as
10 both a stimulant and a hallucinogen.

11 Now, you did discuss that on cross-examination.
12 Putting aside the attractiveness of that combination to youth,
13 as you described, is there any scientific basis, any
14 psychopharmacological basis that would suggest that that makes
15 MDMA more dangerous or more harmful because it is both a
16 stimulant and a hallucinogen?

17 THE WITNESS: I wouldn't say it is more harmful on a
18 neurobiological basis because that gets into a different
19 discussion of how the serotonin and dopamine interact with each
20 other. Serotonin is a modulator of dopamine function, but it
21 does -- and I think this was the intent of the commission -- it
22 does help explain why this drug is particularly attractive to
23 this very youthful population. The entactogenic feature of the
24 drug is very exciting to them. They talk about, oh, when I
25 take this drug, I just feel like I want to hug and love

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1 everybody and it is fun to be around my friends and it is fun
2 to be in that rave scene. This is very attractive to them.
3 You don't get that with cocaine. So you lack that piece of
4 pharmacology, meaning that cocaine would appeal to an older
5 population whereas this appeals to the younger population.

6 THE COURT: You also discussed the fact that dosage
7 amounts are different in the United States than what is
8 typically seen in the Great Britain. Did I understand that
9 correctly?

10 THE WITNESS: Yes. Partially, dosage amounts are
11 different from batches, depending on where they come from,
12 regardless of where they end up. You could argue that there
13 are certain organizations that control the production end or
14 trafficking of the drug and they may make some executive
15 decision that, we want to optimize our profits on this product,
16 so we are going to cut back on Ecstasy. Instead of giving them
17 120 milligrams, we are going to give them 70 milligrams,
18 whatever goes into those kinds of decisions.

19 But if you are getting batches from different sources,
20 then it may mean that the potency of the Ecstasy is different.
21 And as I mentioned before, in some cases, it may mean that you
22 don't have any Ecstasy, even though it is being sold for
23 Ecstasy or it has got something else, it has been contaminated
24 with something like MDMA. Now, MDMA, they are starting to get
25 into dopamine toxicity with MDMA and it starts to look more

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1 like methamphetamine and it does. So depending on where it is
2 coming from there is no Good Housekeeping seal of approval when
3 you buy this stuff. It is illegal, and there is no guarantee
4 as to what it is that you are going to get even within the
5 country you may find different batches with different
6 potencies.

7 THE COURT: In your view, how significant is it in
8 measuring the harm of a drug whether or not the drug has
9 addictive properties?

10 THE WITNESS: Well, it is significant in terms of --
11 if it is addictive, then that means your use is going to be
12 more compulsive and it is going to be less side effect and less
13 negative consequence driven, and you are more likely to use
14 higher dosages, and you are going to do those more frequently.
15 And then you are just getting into the dose-dependent
16 discussion, that is, the more you use, the greater likelihood
17 you are going to pass the threshold for toxicity, and you are
18 going to have problems with it.

19 And the process that leads up to addiction itself
20 generally means you have used the drug quite a bit to get here.
21 Your brain has basically changed. Addiction, we know now is a
22 learned process that is embellished by pharmacology. So you
23 kind of learn to use a drug and make it a part of your life.

24 THE COURT: Would you explain that a little further
25 for me?

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1 THE WITNESS: Addiction is a process of learning. We
2 know now that a lot of the basic neurobiology to addiction is
3 the underpinnings of what learning looks like in terms of what
4 brain systems are involved. Alan Leshner, who is my
5 predecessor at NIDA -- he was the director before I was the
6 acting director -- he used to say that with addiction, what you
7 have done is, you have hijacked the brain. So you have taken
8 advantage of basic neurobiology but you have tailored it in a
9 way that is now harmful to you.

10 So in that regard, you turn what used to be a casual
11 behavior into one that has become a compulsive behavior and now
12 you are going to use more and more of the drug and now you are
13 going to get into the toxic levels of the drug and you are more
14 likely to get things such as we have been discussing with high
15 dose use of Ecstasy.

16 THE COURT: You were present and participated back in
17 2000 and early 2001 when the Sentencing Commission was looking
18 at this. Now you are here today. Can you summarize for me
19 what it is that has changed since May of 2001 when the
20 commission sent its report? You have described in part that
21 some of the technology has improved.

22 THE WITNESS: Correct.

23 THE COURT: What, from a psychopharmacological
24 perspective, have we learned about MDMA since May of 2001?

25 THE WITNESS: I think we have learned that it is

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1 probably quite a bit more complicated than we thought it was at
2 that time, that there are a lot of complexities here. And
3 while our research gives us some answers, there always seem to
4 be confounds there that create some problems in trying to
5 interpret the answers.

6 There is no golden bullet answer to this. There is no
7 one-size-fits-all answer to this. It is very dose dependent.
8 It is very environment dependent. It is probably dependent on
9 the things that people bring to the experience.

10 This is what we call systems biology, and this is sort
11 of a movement of where biology in general is going, but
12 pharmacology is as well. And that is, we have to stop thinking
13 about an isolated exposure of a single system to a single dose
14 of drug and somehow generalize and extrapolate that to reality
15 in life because that is not what life looks like. And that is
16 the case with Ecstasy. There is not one answer that satisfies
17 everything. There is probably a lot of answers that are out
18 there. And in our future, we have to figure out how to
19 integrate it. And for folks such as yourself, you have to
20 figure out how to use this complexity in order to make your
21 decisions.

22 THE COURT: I am always groping down a dimly lit
23 corridor.

24 THE WITNESS: That is why my perspective is fun,
25 because I get to give you the information and then give you the

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1 charge to go ahead and be wise with it.

2 THE COURT: Are you aware of any studies that have
3 directly found neurotoxicity in humans?

4 THE WITNESS: Well, using the definition that I gave,
5 that is, that you have interfered with normal functioning --
6 and there have been a number of them and there have been
7 reports. Some of it is subtle. Some of it is more profound.
8 Some of it is anatomical. Some of it relates to the markers --
9 crude as they are -- of serotonin systems.

10 But in every case there have been other studies using
11 different populations and usually there are some subtle
12 distinctions in terms of how they pick their subjects, how they
13 dealt with those subjects. But in almost every case, someone
14 has come and said, well, in my study we didn't see that same
15 thing. So we are missing something, and I don't think that it
16 is because -- it is not a good guy, bad guy thing. There are
17 good scientists and there are bad scientists. I think that
18 they have just constructed their studies in different ways, and
19 we are not clever at this point enough to know what are all the
20 critical factors and we are not controlling for them and so we
21 are getting these different measures. And that's why the
22 meta-analyses are useful because they allow us to go back and
23 say, while we may not get specific answers, it does tell us
24 that there are a lot of things going on here and we haven't
25 figured out quite how to drill down and come up with the

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Hanson

1 overall answer to what is going on.

2 THE COURT: Thank you, Dr. Hanson.

3 Do counsel wish to make any further inquiries of
4 Dr. Hanson?

5 MR. RORTY: No.

6 THE COURT: Anything further, Mr. Chung?

7 MR. CHUNG: None, your Honor.

8 THE COURT: Dr. Hanson, you are excused as a witness.
9 You may step down.

10 (Witness excused)

11 THE COURT: Does the government have any other
12 evidence to offer?

13 MR. CHUNG: No, your Honor.

14 THE COURT: Does the government rest?

15 MR. CHUNG: Yes, your Honor.

16 THE COURT: Do the defendants have any further
17 evidence to offer?

18 MR. RORTY: No.

19 THE COURT: Do the defendants rest?

20 MR. RORTY: Yes.

21 THE COURT: Two things. One, I made an inquiry last
22 week of the Sentencing Commission staff because I was
23 interested to learn whether they maintained any statistic on
24 the number of MDMA cases sentenced in the United States by
25 year. I could not find that information looking on their web

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1 site and in their compendium of materials that they sent to me.
2 But I was able to speak with a research director at the
3 Sentencing Commission who provided me with a chart titled
4 "Number of MDMA Cases, Fiscal Years 2000 to 2009." And the
5 source is a data file at the commission.

6 Simply so that it is part of the record in this case,
7 in the event that the parties want to refer to it, I have had
8 copies made and my law clerk will distribute them now to
9 counsel. If I had thought of this earlier, I would have
10 distributed them earlier, but better late than never. And this
11 may be dated, as you are already well aware of, but if not, you
12 have got it now.

13 Generally, I would think that one could interpolate
14 from sentencing the recognition that, one, cases take time to
15 be made, indicted and sentenced. And so the tabular data, I
16 think, would correlate well with Dr. Hanson's testimony,
17 albeit, we have about a two-year delay because it revealed a
18 peak in 2003 of 906 Ecstasy sentencings. Thereafter, there was
19 a precipitous decline and it has rumbled around 450 in 2008 and
20 2009.

21 Now, I think I said yesterday that I would afford the
22 parties an opportunity to submit a memorandum to me in
23 connection with this matter after you have had a chance to go
24 over the record. I will give you what time you need, but then
25 I would also like to set this matter down for a sentencing.

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1 Obviously, I have an issue to address here that I am
2 likely going to write on.

3 How much time would the parties like to submit a post
4 hearing memorandum?

5 MR. CHUNG: Your Honor, may the parties have just a
6 moment to confer?

7 THE COURT: Absolutely.

8 (Discussion off the record among counsel)

9 MR. CHUNG: Your Honor, is the Court contemplating
10 simultaneous briefing or sort of more staggered
11 defense-government response.

12 THE COURT: What we could do is have simultaneous
13 submission and then I would give each side a few days to make
14 any short reply to what they saw in their adversary's
15 submission. I think that may be the best way to proceed.

16 MR. CHUNG: OK. One moment.

17 (Discussion off the record among counsel)

18 MR. SPORN: Your Honor, while counsel is caucusing
19 about that, let me tee up one other issue that may or may not
20 affect our scheduling, and that is the custodial status of my
21 client.

22 Absolutely none of us are presupposing any outcome
23 here, but it occurs to us that if your Honor were to find that
24 the guidelines as they are may not be appropriate and find that
25 some other lower guideline would be appropriate, we may end up

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1 in a guideline range, before we ever get to 3553
2 considerations, that approaches the time that Mr. McCarthy has
3 already been in custody. He has been in custody now
4 approximately 14 months.

5 THE COURT: I am well aware of that.

6 MR. SPORN: I know you are, your Honor, and I know
7 that is why you want to proceed to sentencing as quickly as we
8 can, and we want that to and nobody wants him to be in longer
9 than the guideline range. And I have to say that Mr. Chung has
10 not been unsympathetic to that possibility, and we have been
11 talking about it.

12 It was never really contemplated that he was going to
13 be in custody. There were a set of conditions set for his
14 release. We have not been able to meet them. So Mr. Chung and
15 I are now talking again about perhaps tweaking those conditions
16 to perhaps permit his release and, if we can agree, we come
17 with a package or, if not, I may come and make an application
18 because I don't want his status in custody to be a cloud on
19 this inquiry.

20 Obviously, there is a lot of material to digest. We
21 are going to want to marshal all of the facts that we heard in
22 support of our argument, and I am sure that they are going to
23 do the same and this is a time-consuming process, and I don't
24 want your Honor to be in a position of having the fact of his
25 custodial status to be a cloud over your Honor's deliberation.

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1 MR. CHUNG: Your Honor, what I can represent is that
2 Mr. Sporn and I have had discussions regarding this very issue
3 ever since Mr. McCarthy's arrest. And as Mr. Sporn just
4 indicated, there is a bail package set, he just has not been
5 able to meet it.

6 So what I can represent is that the government nor
7 defense has committed to whether that bail package can change
8 or whether an agreement can be made. All that I can represent
9 is that I will continue to discuss on a short-term basis with
10 Mr. Sporn that issue, and if we can come to an agreement, we
11 will come to your Honor with a proposal. If there is an
12 agreement, I am sure that Mr. Sporn will make that application,
13 but we will do that in short order in light of the concern that
14 Mr. Sporn just indicated.

15 MR. SPORN: I am just thinking about it while Mr.
16 Chung was speaking, would it make sense to hold off of setting
17 a sentencing date until we get to the bottom of that?

18 THE COURT: Obviously, if the defendant is able to
19 meet a bail package by agreement with the parties, that takes a
20 lot of pressure off of everyone. I don't sense the same
21 urgency in sentencing his co-defendant who is out that I do in
22 having anyone who is sitting in custody across the street or at
23 the MDC.

24 I would like to hear what the parties have in mind
25 with respect to a briefing schedule.

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1 MR. RORTY: Here is the proposed schedule that assumes
2 that Mr. McCarthy remains in custody.

3 Simultaneous filing on January 21st.

4 Simultaneous responses on January 28th.

5 Sentencing the second week in February. I believe it
6 begins the 5th or 6th. I don't have a calendar with me. And
7 perhaps if the Court does check, I think that the 21st is a
8 Friday. The 28th is a Friday. And we are suggesting
9 essentially somewhere two weeks from then to sentence.

10 But as the Court has said, if the Court is
11 contemplating writing on that, the Court may well want to give
12 itself more time following the completed briefing.

13 THE COURT: Why don't you see if you can talk further
14 about this matter. I really think that my sense was that what
15 you are proposing is an extended briefing schedule. If he is
16 out, in the end, I don't have a problem with that, but I am
17 going to want a little time and I am supposed to begin a
18 three-month criminal trial.

19 I am going to suggest this.

20 Confer, and you can send me a letter in a couple of
21 days and let me know what you propose and whether there is any
22 agreement that can be reached. If not, I will fix a schedule
23 taking into account what you are proposing or I will entertain
24 whatever application the parties wish to bring before me and
25 resolve the briefing then.

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1 Obviously, I am not anxious to impose undue burdens on
2 the lawyers. I think that you have all done a superb job in
3 presenting this matter to the Court. And it has been a
4 fascinating two days and fascinating days leading up to this,
5 reading some of these materials and trying to come to grips
6 with it.

7 I will not fix a sentencing date now. I will expect
8 to get a proposal from you by the 10th of December with respect
9 to a schedule for briefing here.

10 I think you should talk. I think you have been
11 undoubtedly talking for a long time about this matter. It is
12 hot on the skillet, so why not confer.

13 And then if we need to have some resolution of this
14 next week, I can either hear an application, approve a
15 proposal, hear an application. And if I grant the application,
16 fix one briefing schedule. If I deny the application, I am
17 going to fix a more rigorous schedule. All right.

18 MR. SPORN: Understood, your Honor.

19 THE COURT: I am sorry that I can't be more clear with
20 you tonight.

21 MR. CHUNG: I think it has been a lot clearer than
22 some of the issues that we have been discussing, but thank you.

23 THE COURT: Thank you all.

24 Have a good night.

25

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	INDEX OF EXAMINATION	
1		
2	Examination of:	Page
3	ANDREW CHARLES PARROTT	
4	Direct By Mr. Kobre	191
5	Cross By Mr. Michelman	230
6	Redirect By Mr. Kobre	266
7	Recross By Mr. Michaelman	284
8	Recross By Mr. Michelman	299
9	GLEN ROY HANSON	
10	Direct By Mr. Chung	305
11	Cross By Mr. Rorty	342
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		

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Appendix B

2 UNITED STATES DISTRICT COURT
3 EASTERN DISTRICT OF NEW YORK

4 -----
5 UNITED STATES OF AMERICA,

6 PLAINTIFF,

7
8 vs.

No. 13-CR-570 (JBW)

9
10 CHIN CHONG,

11 DEFENDANT.
12 -----

13 August 22, 2014

14 10:25 a.m.
15
16

17 TELEPHONIC DEPOSITION of
18 DR. JOHN HALPERN, M.D., held at United States
19 District Court - Eastern District of New York,
20 225 Cadman Plaza East, Brooklyn, New York,
21 Pursuant to Notice, before CHARISSE KITT, CRI,
22 CSR, RMR, FCRR, a Notary Public of the State
23 of New York.
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A P P E A R A N C E S:

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BY: CHASE A. SCOLNICK, ESQ.

2 MR. SCOLNICK: Good morning,
3 again, Dr. Halpern. This is Chase
4 Scolnick, we're on the record here
5 today.

6 THE WITNESS: Okay.

7 MR. SCOLNICK: Can we start by
8 placing you under oath?

9 THE WITNESS: Yes.

10 DR. JOHN HALPERN, M.D.,
11 called as a witness, having been duly sworn,
12 was examined and
13 testified as follows:

14 THE WITNESS: John Halpern,
15 H-a-l-p-e-r-n.

16 EXAMINATION BY MR. SCOLNICK:

17 Q Dr. Halpern, we have a lot of
18 ground to cover today and I realize you're a
19 busy man, so I want to get started by talking
20 briefly about your qualifications.

21 A Sure.

22 Q Okay. I'm going to just lead you
23 through that in a few questions, so we can
24 kind of just get the substantive matters.

25 Is it true that you're a medical

2 doctor?

3 A Yes.

4 Q And you're licensed?

5 A Yes.

6 Q Did you go to or attend a
7 residency program?

8 A Yes.

9 Q What was that in?

10 A In psychiatry.

11 Q And where was that?

12 A At the Harvard Longwood Psychiatry
13 Residency training program.

14 Q And after completing your
15 residency, were you awarded research
16 fellowships at Harvard?

17 A Yes.

18 Q Go ahead.

19 A I had a Peter Livingston Award and
20 was the fellow from Harvard Medical School for
21 my research, as then I received government
22 funding for my research and my training.

23 Q And since that training have you
24 worked as a director or a psychiatrist in
25 charge of coverage for hospitals in the Boston

2 area?

3 A I am director of coverage for the
4 Division of Alcohol and Drug Abuse at McLean
5 Hospital which comprises all elements of the
6 clinical services we provide for substance
7 abuse and those suffering with mental health
8 issues as well. I also am the director of the
9 laboratory for integrative psychiatry at my
10 institution as well.

11 Q Are you also a professor at
12 Harvard Medical School or associate professor?

13 A Yes. I have a professorship
14 appointment at Harvard Medical School and
15 that's specific to my research of the affects
16 of hallucinations.

17 Q And in your experience with
18 working in hospitals as an alcohol and abuse
19 researcher and counselor, have you encountered
20 people who have been addicted or abusing drugs
21 before?

22 A All the time and pretty much on a
23 daily basis in my work.

24 Q Is it fair to say you've been in
25 contact and interviewed and treated thousands

2 of people who are suffering from drug related
3 issues?

4 A It would be hard to put the exact
5 order of magnitude, but since completion of
6 residency in 1998, I'm sure it's well towards
7 a few thousand people.

8 Q Are you also aware of national
9 statistics and research involving substance
10 abuse issues?

11 A I am.

12 Q And I understand you've been
13 published a number of times in the field of
14 substance abuse and psychologic substances.
15 Is that right?

16 A That's correct.

17 Q And looking at your resume, it
18 looks like probably around 60 different
19 publications, between peer review articles,
20 invited articles and book chapters, abstracts,
21 and letters to the editor. Is that roughly
22 accurate?

23 A That sounds approximately correct.

24 MR. SCOLNICK: Okay. I am going
25 to offer your resume, your CV, excuse

2 me, as Defense Exhibit B to the hearing
3 today, previously provided to the
4 government.

5 (Defendant's Exhibit B1 so
6 marked.)

7 Q Now, Dr. Halpern, I'd like to move
8 on to the substance of your testimony today,
9 and I want to just take a broad picture of
10 what we're talking about before we get into
11 specifics.

12 You're familiar with MDMA, the
13 drug MDMA. Is that correct?

14 A Yes.

15 Q And you've testified about this
16 before?

17 A Yes, I have.

18 Q Are you familiar with the
19 Sentencing Commission's analysis of the drug
20 MDMA conducted in 2001?

21 A Yes, I am.

22 Q And are you familiar with the
23 current state of research regarding MDMA?

24 A There's a tremendous amount of
25 research that is ongoing and published, but I

2 think I'm pretty well versed in the
3 literature, yes.

4 Q Now, you testified before, I
5 understand, that MDMA is a harmful drug. Is
6 that still your opinion today?

7 A Absolutely.

8 Q Okay. Relative to other drugs,
9 specifically cocaine, do you believe that MDMA
10 is more or less harmful than cocaine?

11 A It is my clinical and expert
12 opinion that MDMA obviously is less dangerous
13 than cocaine. No physician could determine
14 otherwise.

15 Q We'll get into that in some more
16 detail. Regarding the state of research and
17 understanding of MDMA, between 2001 and today,
18 how has the understanding and research
19 regarding MDMA's affects on the body changed?

20 A Well, broadly speaking, since 2001
21 there's been a better research system to track
22 humans over time and to have a better
23 understanding of the human/animal dosing rate
24 to, you know, try to compare animal work to
25 human work, primarily by myself, in making a

2 better attempt to control the heat compounds
3 and construct our confidence in earlier
4 studies, and there's definitely better
5 technology since 2001. And that is the result
6 of understanding how MDMA impacts, for
7 example, the serotonin transporter in the
8 brain.

9 Q What was the understanding in
10 2001, for example, involving serts?

11 A Well, it was believed that MDMA
12 would be neurotoxic, would cause a decrease
13 in -- the physical transfer binding would be
14 decreased after ecstasy and it would stay that
15 way. There's evidence that there's some sort
16 of urine toxic event occurring from the
17 substance. And since then we've known from
18 research that with time that sert binding
19 actually return to levels that are comparative
20 to non-users.

21 Q So if I understand you correctly,
22 this data, the scientific community or
23 understanding in 2001 was that there were
24 permanent changes regarding the sert or
25 serotonin levels in the brain after use. Is

2 that correct?

3 A Yes. Particularly it's an
4 important study by Dr. Kish, published in
5 2010, in which using newer or more advanced
6 technology did not find serts in the
7 transporters. And so there's no global
8 massive production of brain serotonin
9 transporter binding. And there's been no
10 substantive study to invalidate Dr. Kish's
11 work.

12 Q You mentioned that Dr. Kish's work
13 found that there was no global mass production
14 in serotonin levels or activity in the brain.
15 What was the understanding regarding that in
16 2001? Was the belief in the scientific
17 community that there was such a global
18 reduction or --

19 A Yeah. There's -- my colleague
20 McCann published in 1998, I believe, claiming
21 that there was loss of serotonin transporters
22 throughout the brain. And so that's -- that's
23 been replaced, I think, with a much approved
24 methodology and a more accurate -- a more
25 accurate sert that was used by Dr. Kish that

2 wasn't available to Dr. McCann.

3 And so the 1998 data that I
4 believe the Sentencing Commission relied on is
5 no longer considered the current scientific
6 conclusion drawn from the literature at this
7 point.

8 Q You mentioned what the -- what the
9 Sentencing Commission considered in 2001. Are
10 you familiar with a document called the -- I
11 believe the SSC or MDMA Report that the
12 Sentencing Commission considered in 2001?

13 A Yes, I am.

14 Q And is it your understanding,
15 based on these new findings and research
16 techniques that you described, that the
17 concerns and fears and research cited in the
18 2001 report has changed significantly?

19 A That's correct.

20 Q And based on those changes, it is
21 your conclusion that the fears and concerns in
22 the 2001 report have not been realized?

23 A That's correct. Not only has it
24 not been realized in basic clinical research,
25 but even looking at public health measures.

2 By now you would be seeing a much different
3 picture from the public health standpoint were
4 those fears to be realized upon those people
5 having significantly abused MDMA.

6 Q And what type of public health
7 measures are you referring to?

8 A Well, back then there were fears
9 that MDMA use would lead to a whole generation
10 that would be depressed or would not respond
11 to antidepressants or would -- there would be
12 a wave of Parkinson's disease, and none of
13 those things have been realized. There was
14 concern about addictive potential, and present
15 we are -- it is obvious that MDMA is not
16 reinforcing, causing crime addiction when, for
17 example, cocaine is. And that, of course, is
18 reflective quite obviously in other measures,
19 such as the government's data on emergency
20 room visits that, you know, close to 200,000
21 people a year showing up with cocaine as a
22 permanent feature in the United States. We
23 have less than, you know, anywhere from 8 to
24 12,000 a year for MDMA.

25 So it's just a dangerous thing for

2 America to present to our communities that
3 cocaine is safer than MDMA.

4 Q Right. I think you mentioned some
5 public health measures and some data from
6 emergency rooms. I think it would be best if
7 we can maybe look at the social metrics
8 involving the two drugs or involving MDMA
9 relative to other controlled substances, and
10 then perhaps we can get more into the
11 scientific research regarding brain activity,
12 memory loss, those types of subjects.

13 So let's start with the relative
14 societal harm caused by MDMA.

15 Are you aware of any studies that
16 have compared the relative societal harms of a
17 number of controlled substances?

18 A Yes. There's been a number of
19 publications on this; most prominently was the
20 work of Dr. David Nut, in England, who
21 published about relative risk across drugs
22 using a methodology assessment of harms. But
23 there's other studies that rank harm of drugs
24 such as, I believe a paper by Dr. Amsterdam, a
25 colleague, that was published in 2010.

2 Another one by Dr. Morgan that was published
3 also that year.

4 And I believe there was a recent
5 study also published that surveyed physicians,
6 asking their opinions, looking at a set of
7 criteria of harmful drugs also.

8 Q Thank you.

9 Now, Doctor, you mentioned a
10 number of studies that were conducted
11 regarding the relative harms of controlled
12 substances. Was there any consensus within
13 those studies regarding their treatment or
14 consideration of the dangers of MDMA?

15 A Yeah. They all ranked MDMA as
16 much less dangerous than cocaine. There's
17 no -- there's nothing offered in the data
18 suggesting otherwise.

19 Q So that would be in each one of
20 the studies you talked about?

21 A Yes.

22 Q All of the studies concluded that
23 MDMA was, would it be fair to say,
24 significantly less harmful than cocaine?

25 A Yes. Exactly what is reflected

2 whenever I speak with colleagues. I surveyed
3 every physician in my division of alcohol and
4 drug abuse, asking them just, you know, which
5 is more dangerous, cocaine or MDMA. To the
6 last physician, exactly the same as what's in
7 those papers, said MDMA is considered safer
8 than cocaine, and it's obvious why.

9 We deal with cocaine, the damages
10 from cocaine abuse on a daily basis. The
11 number of times that we admit people for MDMA
12 abuse is a prominent feature in their
13 admission. This is an extremely rare event.
14 I can't recall even the last time that I have
15 admitted somebody because of MDMA use.

16 Q And in those studies, how did MDMA
17 rank compared to, say, alcohol or nicotine, if
18 you can recall?

19 A It ranked lower than all of those
20 studies. Lower than cocaine and lower than
21 tobacco.

22 Q And do you recall any statistics
23 regarding comparative harms between MDMA and
24 marijuana in those studies?

25 A It was ranked near marijuana. It

2 was ranked slightly higher than marijuana, I
3 believe, by Dr. Morgan and as well as
4 Dr. Amsterdam's paper, and I believe also in
5 Dr. Nut's. But I need to look at Dr. Nut's
6 study again to confirm them.

7 Q That's fine. I'm concerned about
8 the timing here, the date of these studies.
9 Have any of these studies, to your knowledge,
10 been published since 2011, or since early
11 2011?

12 A Yeah, there are studies from other
13 physicians. A few hundred physicians have
14 published since 2011.

15 Q So is it your understanding that
16 this data was not available at the time of the
17 hearing in United States versus McCarthy, in
18 Southern New York?

19 A Yes, that's correct. That's
20 subsequent to the McCarthy Hearing.

21 Q You talked about your own
22 experience, having dealt with thousands of
23 people involved in drug abuse and treated them
24 and also speaking with other doctors in your
25 field. And is it your opinion that there is a

2 consensus regarding the comparative harms of
3 MDMA regarding cocaine?

4 A Yes.

5 Q And what is that consensus?

6 A The consensus is that cocaine is
7 more dangerous than MDMA.

8 Q Okay. I'd like to go on to some
9 example as to why. First, is it your
10 understanding or accepted understanding of the
11 scientific community that cocaine is
12 addictive?

13 A That is correct.

14 Q Is it your understanding, given
15 the current state of research, that MDMA is
16 addictive?

17 A No. It's not showing the
18 reinforcing properties that are exhibited by
19 cocaine. The vast majority of people who
20 abuse MDMA do so in a time limited fashion and
21 do not continue to ingest this in a repetitive
22 pathological way that occurs in cocaine
23 dependents.

24 Q I believe Dr. Parrot testified
25 that MDMA is, quote, one of the least

2 addictive drugs, end quote. Would you agree
3 with that conclusion?

4 A I absolutely enjoy whenever I can
5 agree with Dr. Parrot saying something
6 accurately, and that is one of them. Yes, I
7 agree with that statement.

8 Q Well, we'll get into Dr. Parrot's
9 research in a few minutes, but getting back to
10 cocaine and MDMA. You mentioned that cocaine
11 is addictive, whereas MDMA is not. Given your
12 experience and research in the field, what are
13 the societal harms related to an addictive
14 drug?

15 A Well, it's -- obviously it's
16 dependent on also the direct psychological
17 affects of the drug or the intoxication as
18 well as on the other end of it, just the
19 health consequences that might --

20 So, for example, tobacco.
21 Nicotine is highly, highly addictive and it is
22 one of the leading killers in the world. So
23 it's very dangerous. But in terms of it's
24 impact on cognitive function and general sense
25 itself, it's much less dangerous.

2 So it's more complicated than just
3 those factors alone. Each drug has its own
4 risk profile. But, you know, we look at
5 things like, does it promote morbid illness
6 and does it damage people's functioning in a
7 clinical significant way. And if we just --
8 looking at it from that layman's perspective,
9 what's the clinical upshot of, you know, being
10 an abuser of a drug. You look at measures
11 such as employment, their medical and mental
12 health, and whether there's any observed
13 deference in performance because of that
14 abuse. And without a doubt, cocaine, you
15 know, highly impacts people's lives, whereas
16 we don't see that with MDMA.

17 Q Now, I want to get into that a
18 little bit more. You said that cocaine would
19 affect, certainly would affect people's
20 health. Is that your testimony?

21 A Absolutely. It causes heart
22 attack and stroke and overdose and it leads --
23 it's one of the leading drugs of abuse that
24 land people in the emergency rooms.

25 Q And you've dealt with and treated,

2 I'm assuming, a number of people who have been
3 addicted or having trouble with cocaine.

4 Correct?

5 A Absolutely.

6 Q Is it your experience or is it the
7 scientific consensus in the community that
8 cocaine also has a negative effect on
9 people's, we'll say, family relationships?

10 A Absolutely.

11 Q Could you explain that, please.

12 A Well, because this drug wears off
13 really fast and has an acute craving, such
14 that people will want to continue to use, and
15 so they will spend a tremendous amount of
16 money until they become dependent on it. And
17 this pathological behavior will continue over
18 days and longer. And then there's a period of
19 where they, quote/unquote, crash and then they
20 will wind up doing this again. And the amount
21 of days that they wind up using expands. And
22 the amount of drug they use expands.

23 All of the criteria says they are
24 physiologically and psychologically dependent
25 on the drug even though they know it's

2 destructive, even though they know it's
3 hurting themselves.

4 People who use MDMA do not have
5 such a pattern of abuse. They will typically
6 take, you know, one or more pills on a single
7 occasion and not on successive days, because
8 acute tolerance builds. So somebody who takes
9 MDMA, you know, the very next day, it will
10 have a much more attenuated effect and there's
11 no way to surmount that by taking more.

12 In fact, many, many, many people
13 who consume this drug describe that it stops
14 having the primary desired effects after
15 several uses, and that then self limits how
16 much people wind up going into this phase of
17 life of using. Most people wind up moving on
18 in their lives and stop using MDMA.

19 Q Thank you.

20 Have you noticed through your
21 research or have you noted through literature
22 a relationship between cocaine use, addiction,
23 and crime?

24 A Well, again, absolutely. In one
25 of the clinics that I'm -- that I work at, I

2 also have patients that are in the final
3 stages of release from the Federal Bureau of
4 Prisons, so they're in a halfway house shelter
5 transitioning them, you know, to probation.
6 And I have examined a number of people who
7 were incarcerated because of their crimes with
8 distribution for cocaine. And it's just
9 remarkable how this very dangerous lifestyle
10 will affect our communities. It's a real
11 mess.

12 Q And when you say a very dangerous
13 lifestyle, is that a dangerous lifestyle
14 that's typically associated with cocaine use?

15 A The patients I'm thinking of are
16 people who wind up being abusers of cocaine,
17 who also are involved in the distribution of
18 cocaine illegally. And invariably there's a
19 tremendous history of associated violence,
20 guns and gang collusion in these distribution
21 systems.

22 Q And are those patterns also
23 typical of MDMA users?

24 A No, it's not the same. There are,
25 of course, distribution systems of criminal

2 enterprises that are distributing MDMA, but
3 there's also a much different pattern of abuse
4 and abuse by users themselves, so it's not the
5 same. I'm sure there are criminal gangs who
6 make MDMA sales a part of their enterprise,
7 but there's many people who abuse this drug
8 who seem to believe that within their culture
9 that it's important for them to make
10 additional MDMA available to friends and even
11 family, and it's not about profit.

12 Q Okay. From your experience how is
13 MDMA ingested?

14 A MDMA typically is ingested orally.
15 However, there are people who will also
16 nasally, you know, snort it, and also take it
17 as an enema. I've had a couple of patients
18 who were heavy drug users who also injected
19 MDMA, but the vast majority of people ingest
20 it orally.

21 Q Okay. And regarding cocaine, how
22 is cocaine typically ingested?

23 A Cocaine is typically ingested
24 through snorting powder cocaine or through the
25 smoking of it, freebase, or a cheaper crack

2 variant.

3 Q And --

4 A Some people also will inject it,
5 and some people will inject it as a speedball,
6 so they inject it with heroin. And I myself
7 at the government funded research in which I
8 injected government sourced cocaine to show
9 how cocaine causes local tissue, you know,
10 suppression.

11 For example, the transmission of
12 HIV from needles is more likely, of course,
13 with cocaine, not MDMA. Another example of
14 how dangerous cocaine is, apparently.

15 Q So there is a higher risk of HIV
16 associated with cocaine use than for MDMA use?

17 A I would expect so. Because MDMA
18 is not typically intravenously injected,
19 whereas there is a substantial portion of
20 abusers of cocaine who will use needles.

21 Q Is it fair to say that the vast
22 majority of MDMA users use the drug in pill
23 form?

24 A I'm sure that is certain. I would
25 expect almost 100 percent of people, even

2 those who state that they -- they like to
3 snort it. Even those people who also
4 routinely take it orally as an ingested pill
5 or capsule.

6 Q Is it true that with respect to
7 marijuana, marijuana is typically smoked?

8 A In the United States, yes, it's
9 typically smoked. Other consumption is
10 orally, that people will eat it and swallow
11 it; or some people are not quite smoking it
12 but are volatilizing it. It's heated to a
13 temperature that releases the compounds from a
14 liquid state to gastric without burning it.

15 Q With respect to the vast majority
16 of people in this country who are smoking
17 marijuana, are there any health risks
18 associated with smoking marijuana?

19 A Well, there are. The lungs are
20 not designed for taking vegetative matter and
21 burning it or heating it into our lungs. And
22 so there can be changes to the physical
23 functionality of the lungs and there has -- in
24 the past there was concern that the smoking of
25 marijuana is more dangerous than tobacco

2 because of the tars and whatnot in the
3 cannabis. But important research tends to
4 show -- has borne that out through the work of
5 Dr. Tishkent, the leading expert on lung
6 cancer.

7 And so it was his work -- for
8 example, years ago people would say one
9 marijuana cigarette has the tar of a pack or
10 two of tobacco. And it was his work that most
11 recently showed that marijuana did not promote
12 lung cancer. In fact, we know that cannabis
13 has antitumor properties. And so the extreme
14 concerns about marijuana may be more related
15 to those people that combine tobacco with the
16 cannabis; because cannabis abusers tend to
17 hold what they inhale in their lungs for a
18 longer period of time than somebody smoking a
19 cigarette. So if there is nicotine, if there
20 is tobacco present when somebody is doing
21 that, it makes the exposure to tobacco, even
22 if it's a much smaller amount, much more
23 dangerous for the individual.

24 Q What are the risks associated with
25 inhaling marijuana smoke, including the paper

2 usually used to roll the marijuana into
3 marijuana joints or cigarettes? Is that risk
4 present in the ingestion of MDMA?

5 A No, because it's not -- it's not
6 smoked or consumed like marijuana or tobacco.

7 Q And with respect to ingesting
8 cocaine, as it sounds like the majority of
9 people do in this country by snorting it or
10 inhaling it through your nose, are there any
11 health risks associated with ingesting
12 marijuana -- I'm sorry, ingesting cocaine in
13 that fashion?

14 A There's a number of risks because
15 cocaine is strongly constrictive, tightening
16 of arteries, and that can cause tissue death.
17 That's why some people wind up having heart
18 attacks.

19 Q And are those risks present, to
20 your knowledge, with the ingestion of MDMA?

21 A No, I'm not aware of those risks
22 being present. There is evidence that if MDMA
23 somehow was being ingested chronically every
24 single day, that it will cause alterations to
25 heart valves. And we also believe from that

2 data that it is reversible when the exposure
3 stops. It takes time for the reverse of that
4 damage, but it should occur. But this is not
5 a pattern of ingestion that occurs in humans.

6 Q So if I understand that last part
7 correctly, any damage to the heart associated
8 with MDMA would both be temporary and based on
9 a use pattern that would not be likely to be
10 seen in humans?

11 A That is an accurate summary of
12 what I just said.

13 Q Okay. Now I want to talk about
14 the behavior typically associated with these
15 various drugs. Are you aware of any link or
16 relationship between cocaine use/abuse and
17 violent behavior?

18 A Yes. Cocaine is a powerful
19 psychoactive stimulant. It can induce
20 megalomania behavior, narcissistic overdrive
21 of egos -- a person believes that they are
22 more powerful than they are -- and it promotes
23 aggression. So, yes, cocaine abuse is
24 associated with a higher risk.

25 Q Can the same be said for MDMA?

2 A No. The psychological effects of
3 MDMA are not consistent with any of those that
4 I described about cocaine.

5 Q Now, is there a link, in your
6 experience or in literature, between the use
7 or excessive use of alcohol and violence?

8 A It's extremely well known that
9 alcohol is a very common associated variable
10 to violent crime in the United States.

11 Q Now I want to turn back to the
12 2001 MDMA study that the Sentencing Commission
13 considered. Okay?

14 A Okay.

15 Q Now, that study expressed concern
16 that MDMA use was exploding among late teens
17 and early adults. Is that concern still
18 accurate today?

19 A That concern is not accurate.
20 There's patterns and trends and use, and the
21 government has done an excellent job in
22 surveilling the country year to year to the
23 March of the Future Studies of Johnson and
24 colleagues out of Michigan, as well as
25 substance work with the National Household

2 Drug Use Survey that they've been doing for 30
3 plus years. And, in fact, I believe the
4 Department of Justice issued in 2013 a drug
5 assessment in which the data that I just
6 mentioned showed a decline in use year to
7 year, since I believe the most recent data
8 was -- in that survey was data from 2010 and
9 2011.

10 Q So if I understand you correctly,
11 ecstasy use has actually declined between 2011
12 and today or perhaps between 2010 and 2011?

13 A I believe in 2009, according to
14 the National Household Drug Survey, somewhere
15 around 1.1 million people had tried MDMA, and
16 in 2010 that reduced to roughly, I think,
17 around 950,000; and in 2011 a little bit
18 closer to 900,000, 920,000.

19 So it's gone down year to year.

20 Q So to your knowledge was this data
21 available or presented to the Court at the
22 McCarthy Hearing?

23 A I don't believe that specific data
24 was presented at the McCarthy Hearing, no.

25 Q Is there any information offered

2 by the Department of Justice, in the document
3 you were talking about, regarding the use
4 among teenagers and young adults?

5 A Yes. March of the Future data
6 focuses on surveying drug use of
7 eighth graders, tenth graders, twelfth graders
8 and 12 year olds also. And if I'm not
9 mistaken, I think they quoted data that showed
10 that youth, in general, that there is
11 around -- close to a 4 percent reduction with
12 use since 2010.

13 Q So is it your understanding at
14 this point, if you're trying to interpret all
15 this data, that ecstasy use has peaked?

16 A That ecstasy has peaked and, you
17 know, it has gone downward before and I
18 believe a couple of years it went up a little
19 bit. In general, overall, it's gone down. It
20 has gone down.

21 Q Okay. You mentioned earlier
22 emergency room visits. Is there a way to
23 obtain data regarding emergency room visits
24 for various substances?

25 A Yeah. The Drug Abuse Warning

2 Network, DAWN, is a database, a government
3 database that collects factors involved with
4 emergency room visits and it's just one
5 measure for when we look at that data,
6 specific to drug abuse, it gives us some --
7 some indications of, in the real world,
8 whether a drug is having -- has a dangerous
9 impact on our society as theorized -- as
10 hypothesized in some academic research.

11 Q And have you reviewed the most
12 recent literature regarding emergency room
13 visits for drug use?

14 A Yes, I've looked at this data.

15 Q Could you compare the data for
16 MDMA emergency room admissions to the data
17 related to cocaine and marijuana emergency
18 room related admissions?

19 A Yeah. I believe looking at the
20 DAWN data from, again, 2011, that we had about
21 22,000 emergency room visits, actually, for
22 MDMA. And for cocaine it was actually a
23 little bit over 500,000.

24 Q Based on your research in the
25 field and understanding of the data, is the

2 difference between 20,000 and 500,000 a
3 significant number?

4 A Yes, it's quite significant. In
5 that data, for example, you know, for those
6 emergency room data, you've got about 480,000
7 people showing up with marijuana. You've got
8 350,000 showing up for alcohol. So the fact
9 that there are half a million people showing
10 up for cocaine, the number one drug of abuse
11 associated with emergency room visits that
12 year, I'd say it is very hard to assert that
13 cocaine is safer than MDMA.

14 Q Of the people, of the 20,000
15 people that showed up to the ER related to
16 MDMA use, is there any way to determine how
17 many of them were also using alcohol?

18 A Yes. They also will include
19 alcohol, if it shows up. And I believe it's
20 about 40 percent of the time that alcohol was
21 present as well. And that's important,
22 because we know from some basic science work
23 that exposure to alcohol, with the presence of
24 MDMA, increases the blood level of MDMA.

25 And so a person may think from

2 prior experience that they have taken a,
3 quote/unquote, safe dose from their experience
4 of MDMA, even from a pill, a set of pills that
5 they have used previously, but in the presence
6 of alcohol there can be as much as a
7 20 percent increase in MDMA availability in
8 the bloodstream.

9 Q Okay. You talked about the visits
10 related to just these drugs at the ER. Is
11 there any way to determine or is there any
12 measure available to determine a percentage or
13 rate of self harm on these drugs? For
14 example, suicide or suicide attempt rates
15 related to these drugs?

16 And if that's not a clear
17 question, I can rephrase.

18 A So I believe that there is such
19 data on the -- on drug related suicide
20 attempts, that's part of why the non-database
21 exist. And so that ratio is calculated in the
22 database itself and so it gives a sense of
23 relative risk.

24 For cocaine it is a factor of
25 18.9, and with higher numbers the more

2 dangerous the risk. And it is not listed,
3 though, for MDMA.

4 Q And what does that suggest to you,
5 the fact that MDMA is not listed?

6 A That it's so rare and so -- it's
7 statistically near zero, as opposed to
8 cocaine, which basically, you know, is
9 significant.

10 Q Thank you. I'd like to turn now
11 to your field of research, as it stands now,
12 regarding potential damage or changes to the
13 brain secondary to MDMA use.

14 A Okay.

15 Q Have you heard the term
16 neurotoxicity before?

17 A Yes.

18 Q What do you believe the definition
19 of neurotoxicity is?

20 A Well, it's ill-defined and it is
21 one of these terms used loosely in scientific
22 literature. It's very hard to differentiate,
23 for example, brain change from brain damage.
24 And one of the most important ways to look for
25 evidence of toxicity is showing that there's

2 some functional impact that can be associated
3 to the use of a drug or patterns of behavior
4 of other substances. And so -- but for me I
5 would say probably one of the most important
6 ways of looking at neurotoxicity would be
7 actually neuron death, the killing of the
8 actual cell. MDMA is not associated with
9 killing.

10 Q So if we're using the definition
11 of -- applying the definition of
12 neurotoxicity, if we use the definition of
13 neuron death, does MDMA have a neurotoxicity
14 effect?

15 A If we're saying neuron death, the
16 answer would be no, it does not do that.

17 Q Let's broaden it a bit and talk
18 about significant cognitive impairment. Have
19 you done any research regarding whether MDMA
20 use at any level causes significant cognitive
21 impairment?

22 A Yes.

23 Q Can you tell us about that
24 research?

25 A Yes. I've completed one of the

2 largest studies ever. And the most -- really,
3 the largest study of its kind, funded by the
4 National Institute of Drug Abuse on removing
5 the types of damaging compounds in the
6 literature that exist that are highly
7 problematic in almost all the other
8 literature. So it was a more tightly designed
9 study fixing the methodological failures of
10 what existed in the literature, as well as
11 being almost sort of a magnitude larger. It's
12 the largest study that's completed, I believe,
13 in the United States.

14 Q Okay, let me stop you there,
15 because I want to break that down a bit.

16 You mentioned compounds. How
17 would you explain that word, compound? What
18 does that mean?

19 A In general, there is never a
20 perfectly designed study. And while lawyers
21 may pick apart this weakness, that weakness,
22 in science we know it's virtually impossible
23 to design a perfect study. And so those
24 problems can be so significant as to decrease
25 our confidence in the value of the findings.

2 So there's no compounds, in a sense that
3 compounded data may invalidate the data,
4 there's even unknown compounds, things we
5 don't know is doing what.

6 But there are things that are
7 obvious to science that would make for a
8 stronger study, and some of these things were
9 not attempted prior because people have
10 assumed that it would be near impossible to
11 do; whereas, with funding from the government
12 we were able to importantly evaluate this
13 question again of what's the cognitive impact
14 of MDMA.

15 Q Okay. So in the interest of time,
16 I'll ask you some more pointed questions about
17 compounds. It sounds like basically what
18 you're trying to do with these studies is to
19 determine the effects of MDMA on cognitive
20 functioning. Is that right?

21 A As best as we can for the study,
22 yeah.

23 Q Now, it sounds like this is
24 something that could be difficult to do. Is
25 that fair to say?

2 A That's correct.

3 Q And is that because it's --

4 A Well, because the very best and
5 most accurate way would be that you have a
6 study subject staying within a laboratory, and
7 then we give them a known amount of pure MDMA
8 and we do that over time, and then we control
9 all those factors. We know how long they're
10 sleeping for. We know that they're not
11 ingesting other substances. And we know that
12 they truly are ingesting MDMA.

13 So using drug users from the
14 community is less accurate than doing that.
15 Obviously there's ethical problems with doing
16 what I just described. So we do the next best
17 thing. We use real world users for these
18 tests.

19 Q Are there problems associated or
20 compounds associated with questioning drug
21 users in the community, without bringing them
22 into a laboratory?

23 A There's multiple. And those
24 problems are not addressed by the vast
25 majority of the literature. Those problems

2 are inadequate control for sleep deprivation.
3 Because people who are users go to all night
4 dance parties. And if they go and get tested
5 while they're sleep deprived, we know that
6 they will do worse; whereas, a comparative
7 group of, say, college-age kids that are going
8 to parties well rested, they wind up doing
9 better. Not because they're free from ecstasy
10 exposure but because they're better rested.
11 Another would be inadequate control for other
12 drugs of abuse, an inadequate washup period
13 from last use.

14 The failure to do drug testing and
15 the kind of neuro cognitive testing that would
16 ensure that the person hasn't ingested MDMA in
17 the prior three days and haven't recently used
18 other drugs of abuse, you can do a hair
19 analysis for drugs, to both confirm the
20 presence of MDMA, and also the absence of
21 other drugs, just to confirm the histories
22 that they provided in their psychiatric
23 interview.

24 Q Okay, let me stop you there.

25 Have other researchers tried to

2 control or exclude these compounds from their
3 studies?

4 A As far as I know, my two studies
5 are the only ones of the kind that addressed
6 all of those elements.

7 Q And are there other studies that
8 perhaps have -- strike that.

9 Is there an additional compound
10 related to prior drug use? If we're talking
11 about brain imaging, how would prior drug use
12 before any involvement in the clinical study,
13 how would that be a possible compound?

14 A A significant one. Because we
15 know that the drugs of abuse do impact on --
16 on the brain. And so if these imaging
17 studies, poly drug abusers, one group who have
18 used more ecstasy than the other group or the
19 other group is poly drug abusing and hasn't
20 used ecstasy, that is not the same thing as
21 evaluating somebody who's just been exposed to
22 ecstasy, so that we can narrow it down and
23 have a pathology to identify ecstasy.
24 Instead, we have a question as to how much
25 confidence do we have in these statistical

2 measures that are used to control for that
3 compound.

4 Q You mentioned that you did one of
5 the largest studies of this kind or perhaps
6 the only study with MDMA that removed or
7 accounted for these compounds. What were your
8 results? Could you discuss your findings?

9 A So in a data of a couple of
10 hundred people, all were from the dance party
11 scene, we found no difference in cognitive
12 performance on any of the exhaustive measures
13 administered when we compared globally the
14 users to the non-users.

15 When you do a post testing split
16 of the data to create a group of moderate
17 users of MDMA, those who have used it 20 to 55
18 times and those that are characterized as
19 heavy users, those who have used it
20 essentially more than 50 times, several times
21 in their life, we do find some differences in
22 performance, impulsivity and some other
23 measures, like the finger tapping test.

24 But what's interesting is a number
25 of them showed some trends or statistical

2 significance only in the moderate users, not
3 the heavy users. And so that really reduces
4 our concern that what we're finding is
5 associated then with MDMA, maybe due to
6 another factor not yet identified. But, in
7 fact, the first study that we had published
8 found impulsivity, and that concern is
9 associated with the function of serotonin
10 turnover, and we did publish on that. But
11 then when we got -- and that's like 20, 30, 40
12 people, like most of the other literature out
13 there that finds problems. But when we
14 greatly expanded the study to a couple hundred
15 people to peer that finding, it didn't hold.

16 So you can have sometimes these
17 statistically significant findings, but it may
18 be a function that data is compound. In
19 almost all of the literature, you know, ten to
20 40 people, it may be inadequate for capturing
21 the truth. You may find the people that are
22 initially screened are the ones having the
23 most problems or the most curious to volunteer
24 for studies is a compound that you wouldn't
25 even consider unless they're trying to get a

2 much larger data set, which fortunately
3 neither would be of importance to obtain.

4 Q So if I understand that correctly,
5 Doctor, you did at least two studies regarding
6 subjects in their use of MDMA and cognitive
7 effects. Correct?

8 A Yes, with relatively pure users of
9 MDMA who had little to no exposure to other
10 intoxicants, including alcohol.

11 Q Now, how did the findings -- you
12 mentioned impulsivity and finger tapping
13 tests. How did your findings from the first
14 test differ from the --

15 A First people showed some of the
16 measures on the -- on a test measure that
17 actually is designed for evaluating brain
18 trauma used prior to -- prior to our work
19 for -- with drug abuse. But some of the
20 measures showed an impulsive strategy in
21 attacking the procedure of basically sorting
22 cards and counting them in a timed fashion.
23 But in a larger study it wasn't replicated, it
24 did not show that. This work is relatively
25 exclusive to users of ecstasy, and actually

2 was done twice by us, two different studies.

3 Q So based on your two studies, if
4 we can extrapolate some conclusions from that
5 regarding the use of MDMA, moderate to what
6 sounds like fairly high use of MDMA, did you
7 conclude that there is significant deprivation
8 or significant decline in cognitive
9 functioning, secondary to MDMA use?

10 A No, we did not find any ominous
11 concerning results. We did not find anything
12 that would support that there is a clinically
13 significant or a functional impact on
14 performance by those individuals who
15 participated in this work from MDMA.

16 Q Was this work published in a peer
17 review journal?

18 A Both were published in peer review
19 journals. I believe the first one was
20 published in Drug and Alcohol Dependents and
21 the second one was published in Addiction, two
22 of the top journals of substance abuse in the
23 field of research.

24 Q Now, with respect to your second
25 article, that was the one that was published

2 in Addiction. Correct?

3 A Correct.

4 Q The government has put forth
5 before the Court an exhibit, a response to
6 your position from -- it looks like that was
7 also published in that journal. Have you
8 reviewed that?

9 A Of course.

10 Q And have you replied to that, in
11 the journal?

12 A Yes, we did.

13 Q Was the reply published?

14 A You know, we explained quite
15 clearly. I mean, I can go through it point by
16 point, if you want. But we had the last word,
17 in a sense. None of those authors decided to
18 try to retackle what we understood our data to
19 show.

20 Q Let me stop you there, just
21 because some of us are not familiar with the
22 field of research in publications. A peer
23 review journal allows responses and rebuttals.
24 Is that fair so say?

25 A That's correct.

2 Q Okay. So there was a response to
3 your position and that was the one that was
4 put before the Court as an exhibit. You
5 replied to that. Correct?

6 A Yes. And any legitimate fact
7 finder has to review all of that. You can't
8 just pick and choose what you like. You can't
9 cherrypick. You can't just cite letters which
10 are not -- which is not actual research,
11 trying to pick apart our findings and then
12 fail, utterly fail to evaluate our response to
13 those letters. That's basically below
14 standard, I would say, for any expert witness
15 to do. That's just not competent work.

16 Q And your response was published in
17 what year?

18 A It was published right alongside
19 those letters.

20 Q Okay.

21 A So in 2011 our response to
22 Dr. Parrot, Dr. Kish, and Dr. Rogers, are
23 comprehensive responses to the issues that
24 they raised, appeared right alongside their
25 letter. So anybody who would cite those

2 letters and not take the time to evaluate our
3 response is -- should call into question
4 whether anything should be believed by that
5 person, in my opinion.

6 Q Have there been any new studies
7 involving new -- new participants, new data
8 stats, new brain imaging, new comprehension
9 responses is what I'm getting at, since your
10 2011 study involving the cognitive effects of
11 MDMA?

12 A There has been one study in the
13 Netherlands, of college kids, both prior to
14 drug use and the years to follow. We
15 interviewed them and then identified those
16 people who were new to ecstasy. And so there
17 has been some additional work published since.

18 Q Since you published your 2011
19 article?

20 A I believe the next MDMA data was
21 published roughly around the same time, 2011,
22 and then forward.

23 Q Doctor, are you familiar with a
24 researcher whose last name is Parrot, in the
25 field of MDMA research?

2 A Yes, I know him well.

3 Q And has he published anything
4 since 2011 regarding MDMA use?

5 A Yes. He is often writing opinion
6 pieces and reviews and I believe offered
7 another review that was published in 2013.

8 Q I want to talk to you about that
9 review in 2013. You've read it before?

10 A I have.

11 Q Is this review based on any new
12 studies? And what I mean by "new," I mean
13 after 2011?

14 A No, it's not.

15 Q Is it just a review of studies and
16 literature that was published before 2011?

17 A That's correct.

18 Q How has that paper been accepted
19 in the scientific community?

20 A Well, something remarkable and
21 very rare has happened. The Human Psychology
22 received for peer review a very detailed
23 critique of Dr. Parrot's 2013 paper,
24 completely taking him to task for that
25 review's failure to address fully the

2 literature and cherrypicking over studies that
3 would be in opposition to the points that he
4 was raising and that had led to his
5 miscitation and/or misdescription of other's
6 work. That was published recently, in 2014.

7 MR. SCOLNICK: Okay. Before we
8 get into that in more detail, I'm
9 offering into evidence now what's
10 Defendant's Exhibit B, which is your
11 response to Parrot, Fisk and Rogers et
12 al. I've given a copy of this to the
13 Government.

14 (Defendant's Exhibit B so marked.)

15 Q Moving on to what we just talked
16 about, this article that was published,
17 critiquing or criticizing Parrot's work. I
18 quote, Parrot's review frequently exaggerates,
19 misrepresents or omits research findings.

20 Are you familiar with that
21 provision in this 2014 article?

22 A Yes. And I'm stunned when reading
23 it. Because normally -- you know, very
24 specific language like that is reserved for an
25 editorial or a letter to the editor, but this

2 actually appears within a peer reviewed
3 article. So I took greater significance from
4 that, especially since published in the very
5 same journal that Dr. Parrot's 2013 review was
6 published in.

7 Q Is this the latest word, this
8 article that we're talking about here, on
9 Parrot's research?

10 A I believe so.

11 MR. SCOLNICK: I'd like to offer,
12 as Defendant's Exhibit C, an article
13 entitled: A Reconsideration and
14 Response to Parrot 2013, quote, Human
15 Psychobiology or Ecstasy, an overview of
16 25 years of empirical research. And
17 this has been provided to the Government
18 before today.

19 (Defendant's Exhibit C so marked.)

20 Q Do you agree with the conclusions
21 of this 2014 article?

22 A I do.

23 Q There have been a number of
24 studies that have found some brain changes
25 relating to MDMA. Correct?

2 A Correct.

3 Q And to summarize your
4 understanding of the state of the field right
5 now, is there any research, reliable research
6 or findings that have confirmed significant
7 cognitive impairment secondary to ecstasy use?

8 A I'm not aware of any research that
9 shows clinically meaningful impairment from
10 MDMA abuse.

11 Q Could you explain that, what do
12 you mean by clinically -- significant, I think
13 you said?

14 A Clinically meaningful. So
15 something that can take on statistical
16 significance. The fact that a person may
17 perform a few milliseconds to a few seconds
18 slower than somebody else may take on a
19 statistical significant study, that the
20 difference between the two really identifies
21 one group over the other. But that -- but
22 both measures, both results could be in the
23 functionally normative range of performance.

24 So merely finding that we have a
25 statistical significant decrease in

2 performance is insufficient to take away a
3 message that MDMA will damage your performance
4 in everyday life.

5 Q I only have a few more questions.
6 We need to turn it over to the Government to
7 give them an opportunity to question you here.
8 But regarding these findings, the clinically
9 insignificant decrease in performance.

10 Are there any other drugs, legal,
11 either by over-the-counter or prescription
12 drugs, that have a similar effect; meaning,
13 decrease in performance to MDMA?

14 A Yes.

15 Q Could you explain what those drugs
16 are?

17 A Well, for example, much has been
18 claimed that MDMA use may cause verbal memory
19 deficits, with other measures of how we access
20 language. And we already know that Vicodin,
21 Clonidine, those sorts of drugs, all of them
22 do that. All of them can cause verbal memory
23 deficits. In other words, if we're concerned
24 about, like I said, neuron death, alcohol
25 causes neuron death. I don't know if I can

2 clarify that, but MDMA does not cause neuron
3 death.

4 Q Now, comparing MDMA to alcohol,
5 would you say that alcohol causes
6 significant -- significantly more brain damage
7 than MDMA?

8 A Well, having done a different
9 study, looking at the long term neurocognitive
10 functional consequences, in this case its
11 comparison of those who follow the native
12 American church. One of the comparison groups
13 was native Americans who had been daily heavy
14 drinkers of alcohol and were now sober. And
15 there has been extensive and exhaustive
16 literature showing significant cognitive
17 damage from alcohol, all of which is nowhere
18 near realized in any of the data for MDMA.
19 It's just remarkably damaging to cognitive
20 function when a person is pathologically
21 addicted to alcohol.

22 Q Thank you. Just one other area.
23 In 2011 the judge in the McCarthy
24 case was concerned about the fact that MDMA
25 was, I believe the quote was, aggressively

2 marketed to children and young teens. I might
3 be misquoting it, but that was the idea.

4 Do you think that that concern is
5 still a valid one at the present time?

6 A Well, marketed, you know, how and
7 by who? Since 2011 electronic dance music has
8 become more popular. Some of that music has
9 messages of drug use. It's quite typical in
10 pop culture to include the use of MDMA. But
11 that's not marketing specific to entice people
12 to use, you know, by drug dealers.

13 But separate from what's popular
14 in entertainment, I would say no, it's not
15 aggressively marketed, if -- or it's
16 ineffectively marketed. Because as we started
17 out with -- with earlier questions, we have
18 government data showing that use has
19 decreased, not increased.

20 Q And in your experience dealing
21 with teenagers or young adults who are abusing
22 MDMA, is it your experience that they have
23 used marijuana at the same time or prior to
24 using MDMA?

25 A It is quite common that people

2 will have abused multiple drugs. The
3 consumption of alcohol from the age of 21 is
4 also an elicited activity. It's to be expected
5 that most youth will have broken the law and
6 gotten intoxicated with alcohol as well. So,
7 yes, since marijuana is the most abused
8 elicited substance, other than alcohol, it
9 would be common to expect that they've also
10 been smoking marijuana.

11 MR. SCOLNICK: Thank you. And
12 then just before we finish, I want to
13 admit as Defense Exhibit E, the study
14 discussed from Scotland which is
15 entitled: Quantifying the RR of harm to
16 self and others from substance misuse:
17 Results from a survey of clinical
18 experts across Scotland. That was the
19 article --

20 THE WITNESS: I'm sorry, I forgot,
21 yeah.

22 MR. SCOLNICK: Okay. And with
23 that, I turn it over to the Government.

24 (Defendant's Exhibit E so marked.)

25 EXAMINATION BY MS. MOORE:

2 Q Good morning.

3 A Good morning.

4 Q I just want to clarify a couple of
5 matters you discussed with Mr. Scolnick.

6 You mentioned emergency room
7 visits. Were the numbers that you gave us
8 total visits? For instance, the 22,000 for
9 MDMA, that would be total emergency room
10 visits?

11 A This is looking at the most recent
12 non-data that was published, yeah. So this is
13 from --

14 Q To total reported visits?

15 A -- 2011, drug related emergency
16 department visits.

17 Q Those were the total reported
18 visits?

19 A Total reported visits to the
20 emergency room department for any illicit drug
21 for that year was ranked at 1,252,000.

22 Q Okay. And then for each of the
23 drugs, the number of visits that you gave us
24 was just the total visits not a percentage of
25 users of that drug who had visited the E.R.

2 Correct?

3 A There is both the wrong number of
4 emergency department visits, as well as a
5 percent of E.D. visits. The numbers that I
6 was using was the number, not the percent.

7 Q But the percent you're talking
8 about there, is the percent of total emergency
9 room visits for one particular drug, not
10 percentage of users of a drug who end up in
11 the emergency room. Correct?

12 A That's correct. In order to do
13 that, what we could do is look at the National
14 Council Survey data of total users estimated
15 in the country, and then we could factor in
16 the number of emergency room visits to that
17 number to get an estimate of how many users
18 overall wind up in an emergency room. And I
19 believe that number would be quite small for
20 MDMA in comparison to cocaine.

21 Q Do you have that data?

22 A The government doesn't publish
23 data that crosses it. I actually have
24 chapters I wrote. I think I actually did do
25 that comparison. It's not at my finger tips.

2 But I remember from my numbers that I just
3 described, that MDMA was much, much lower than
4 cocaine.

5 Q You mentioned before, when you
6 were discussing cocaine, powdered cocaine
7 versus crack cocaine, when you were discussing
8 cocaine more broadly during your discussions
9 with Mr. Scolnick, was your use of the word
10 cocaine exclusive to powdered cocaine or was
11 it including both: The powder and the crack?

12 A It included both.

13 Q I'm sorry, I couldn't hear you?

14 A Yes, both.

15 Q So every time you talked about the
16 harmful nature of cocaine, you're talking both
17 powdered cocaine and crack cocaine?

18 A That's correct. They're both of a
19 significant greater risk, in my opinion, than
20 MDMA, whether you separate them or not.

21 Q Turning to your 2011 study. The
22 median lifetime uses of MDMA in your study was
23 43.5. Right?

24 A Correct.

25 Q And are you aware that other

2 studies have suggested that MDMA users take
3 approximately 200 tablets over a lifetime.
4 That's average?

5 A That's the number of instances of
6 MDMA ingestion, that's not the number of
7 pills.

8 Q Do you have a number for average
9 use of pill usages?

10 A If you give me a second I can give
11 you that data. I'm still looking for my
12 actual paper. So data published in 2011 just
13 offered the number of separate instances. The
14 median number of pills, I'm fairly certain it
15 was over 100 pills. I'm looking to see if
16 it's also in our response to Dr. Parrot. I'm
17 not finding it. But it was significant. It
18 was certainly of a similar magnitude of pills,
19 especially heavy users.

20 Q Okay. That's fine.

21 A I'm sorry. I believe our largest
22 user had ingested MDMA on more -- with more
23 than 400 pills.

24 Q Okay. Are you aware that Kish
25 published a study in 2010 and found that MDMA

2 results in toxic outcomes to serotonin neurons
3 within the cortex and hippocampus among other
4 areas?

5 A I'm aware that Kish -- that the
6 Kish 2010 imaging study have, yes, decreased.
7 But importantly, unlike what was found on
8 McCann in 1998, there is an official serotonin
9 transporter throughout the brain and that's in
10 the very same paper that you cited. And then
11 if you turn to some of the other researchers
12 that show that sert can rebound over time
13 because there's a very large range in the sert
14 binding. So, again, what's -- the fact that
15 there's a declarant like that found is enough
16 to serve that its of clinical importance with
17 some drugs that do much the same that are --
18 that are actually approved.

19 Q Okay. Were you aware that McCann
20 published a 2008 piece that found a
21 correlation between reduced sert binding and
22 neurocognitive deficit in MDMA user's
23 maintenances?

24 A I am aware of that paper but we
25 also know that sert binding detriments are not

2 permanent.

3 Q Okay. Are squirrel monkeys
4 closely related physiologically to humans with
5 regard to metabolizing MDMA?

6 A We know that using monkey primates
7 is for clinical, for preclinical research is
8 going to give more, in general, more accurate
9 data for us, and that the metabolic -- the
10 metabolism of MDMA in nonhuman primates is
11 going to approximately give a use.

12 Q Okay. And are you aware that in
13 testing the effects of a single oral dose of
14 MDMA, Cowan et al in 2007 found that it
15 produced a significant dose related depletion
16 of serotonin and metabolite 5-HIAA in the
17 cerebral cortex, hippocampus, and thalamus of
18 the squirrel monkeys?

19 A Sure. Using doses that might not
20 scale to human, because we wanted animals to
21 actually give a dose that will achieve a toxic
22 finding. But that doesn't mean that it is
23 consistent with what most humans do in their
24 abuse of the drug. And also it's -- what's of
25 interest is what happens over time. We could

2 survive acute exposure of the brain to a
3 substance that's going to alter brain function
4 and brain chemistry during testing. During
5 that acute phase it's most likely to realize
6 detriments in performance and detriments in
7 brain measures such as that. But what happens
8 over time, what's the functional significance
9 of that? That's the more pressing question,
10 in my opinion.

11 Q Okay. Well, are you aware that in
12 2010 Kish published a study examining users of
13 approximately 200 lifetime doses of MDMA and
14 found that there is an inverse relationship
15 between the length of MDMA use and sert
16 binding reduction?

17 A I'm aware of his findings. I'm
18 also aware that Dr. Kish is -- I mean, I hate
19 to put words into his mouth. Let me just be
20 accurate about this. Kish is not raising red
21 flags that we've got a dangerous and
22 neurotoxic drug in MDMA even from his 2010
23 findings. Maybe Dr. Parrot is somebody who
24 likes to cherrypick like that. But no, even
25 Dr. Kish does not validate that conclusion and

2 nowhere does any physician say that it is as
3 dangerous as cocaine. So it's very
4 concerning. It's a very concerning thing.

5 Q Are you aware that this study
6 identified deficits including -- and forgive
7 me, I'm probably going to pronounce this
8 wrong -- serotonergic neurotoxicity?

9 A Well, fortunately it doesn't do
10 the neurotoxic thing that alcohol does of
11 actually killing brain cells. So what we call
12 reformation of detriment extending from
13 serotonin after exposure from MDMA to be,
14 quote/unquote, neurotoxic if you want to do
15 that. But those very same changes in monkeys,
16 in humans, were well known by FDA when they
17 considered and approved the drug phenformin,
18 which was at market. So those very changes
19 that you're describing right now have in the
20 past been considered by the FDA and they still
21 went ahead and approved the drug any way.

22 Because when you have known
23 medical benefits for a drug, you can also give
24 a form of consent that there may be some
25 problems. There's many drugs that cause some

2 inherent cognitive function. If you're dying
3 of brain cancer and I give you a highly toxic
4 dose of chemotherapy that gives you five more
5 years of life but shaves five points off your
6 IQ, I bet you take it.

7 We're not going to prevent you
8 from having that life-saving drug even though
9 it may impact your cognitive performance. We
10 have a drug that doesn't have any supplemental
11 utility. Any of these findings from a
12 clinical perspective can be milked by those
13 who want to lie to the public in asserting
14 that actual MDMA is a greater danger to our
15 public health than cocaine.

16 Q Are you aware that Jacobsen, in
17 2004, showed that MDMA users had demonstrated
18 abnormal function of the hippocampus during
19 memory function tests?

20 A I would need to see that actual
21 paper just to refresh my memory. I'm sure
22 what we're looking at, all these studies with
23 tons of compounds in them, in a control for
24 past drug use and incentivized that's rather
25 small in making it very difficult to

2 extrapolate risk for the public at large. But
3 sure, I'm -- I would expect that there can be
4 such findings, yes.

5 Q Okay. And are you aware that
6 Von Geusau, in 2004, also showed significantly
7 worst performance of male MDMA users on task,
8 that correlate to cognitive flexibility and on
9 the combined executive function test?

10 A Yeah, and that's an example of the
11 type of weak literature that exist. Why we
12 were funded to do the work that we did. You
13 know, obviously if I had just found more harm,
14 it would have been great for me to get more
15 funding to just continue to do that. But I
16 just honestly published my findings that we
17 had. But small studies like the one you just
18 cited are not of significant value compared to
19 my own published work.

20 Q All right. Are you aware that
21 Jager, in 2008, found using the FMRI, that
22 MDMA was associated with reduced associative
23 memory performance?

24 A Again, there are multiple
25 compounds in that work that show they were

2 removed to have real confidence. That what we
3 have is a finding of public health
4 consequence. It's concerning, there's no
5 doubt about that. But what's the functioning
6 take home message from it, is it's still
7 controversial. And the fact that this
8 controversy has remained for such a long time
9 points to the weakness of the underlying
10 argument that MDMA is the clear and present
11 danger as being attempted by the government
12 still, and quite sadly.

13 But it's important for -- I mean,
14 put it this way: I have yet to interview a
15 single drug user that thinks that a drug is
16 safe. No user thinks that. But this message
17 is being promoted that if we talk about
18 relative risk then we may be assuring safety
19 to some people. I have never, I have never
20 once said that MDMA is safe. I prefer that
21 people don't abuse drugs, including MDMA.

22 Since we're in a world where
23 people can still obtain them, we have to
24 accept that some drugs are going to be more
25 dangerous than others and it would be wise for

2 us to target those drugs that are doing the
3 most damage to our society, which we're not
4 quite doing.

5 Q Are you aware that according to
6 NIDA, affects of acute or short-term cocaine
7 use are usually reserved to clinical symptoms?

8 A I didn't hear the second part.
9 Are usually what?

10 Q Reserved to clinical symptoms.

11 A I'm not sure what you're saying.

12 Q Such as tachycardia or seizures or
13 increased blood pressure, things like that.

14 A Or as I described, you know,
15 having a heart attack also causes cognitive
16 deference in performance, in carrying oxygen
17 to the brain. So from a medical standpoint as
18 a physician, we can -- what we care about are
19 the actual people and whether the risk is
20 directly related to the drug or indirectly
21 related through the pattern of abuse. In the
22 end it's still harming the same person.

23 And when we look at that real
24 world situation, there's not a single
25 physician I know of who would ever agree with

2 the government's position or the U.S.
3 Sentencing Commission's position that cocaine
4 is a substantially safer drug from MDMA. This
5 may be one of the most dangerous public health
6 messages that the government is allowing to
7 continue to stay.

8 Q Are you aware that taurine is a
9 neuro-protective amino acid that reduces the
10 excitatory actions of the brain and protects
11 against -- excuse me, I'm probably pronouncing
12 this wrong -- dopaminergic neurons?

13 A Dopaminergic neurons, yeah.

14 Q And are you aware that
15 Yablonski-Alter, in 2009, found that while
16 neurophysiological changes can begin to occur
17 following continued use of cocaine, repeated
18 cocaine administration also results in the
19 release of taurine?

20 A Which that points out to just how
21 toxic cocaine is since we see victims of
22 stroke induced from cocaine and from people
23 after their heart attacks, that the brains
24 aren't functioning like they used to. That
25 points out even more how dangerous cocaine

2 must be that it can release something
3 neuro-protective and yet we see clinically all
4 the time these severe damages from cocaine
5 never, never seen on a routine basis like
6 cocaine with MDMA. It's really sad.

7 Q Were you aware that subsequent
8 cocaine use has been shown from Nestler, in
9 2005, to result in an increase in dendrites?

10 A I guess that would be an example
11 of neurotoxicity. Right? Because that's
12 brain change. You can't just cherrypick and
13 say that the reformation of dendrites from
14 neurons, MDMA, causes brain damage when you're
15 now citing a paper.

16 So to repeat myself, if we follow
17 the logic that alteration of the expression of
18 dendrites from MDMA is, quote/unquote,
19 neurotoxic, then the alteration of dendrites
20 from cocaine to increased expression of
21 dendrites, this too must be an example by that
22 definition of neurotoxicity.

23 Q Turning to the paper that you
24 spoke with Mr. Scolnick briefly about, it's
25 titled: The Reconsideration and Response to

2 Parrot, best beginning of it.

3 Are you aware that the authors of
4 this piece listed a conflict of interest in
5 their paper?

6 A Yes.

7 Q Because two of the authors are
8 affiliated with MAPS as the executive director
9 and as a clinical research and information
10 specialist. Right?

11 A Yes, I'm aware of that.

12 Q And are you aware that developing
13 MDMA into an FDA approved prescription is MAPS
14 top priority?

15 A I can't speak to their -- their
16 direct agenda or top priority, since I'm not a
17 member, a person who is running MAPS or
18 anything like that. I'm not a MAPS
19 researcher.

20 Q Are you aware that that is
21 something that MAPS is interested in, whether
22 or not --

23 A Oh, yeah, of course. Of course.

24 Q And then turning to the Nut piece.
25 In that article you're aware that the

2 researchers discussed the limitations in their
3 papers. Right?

4 A All good studies should do that,
5 yes.

6 Q And in this paper the authors
7 noted that many of the harms of drugs are
8 affected by their availability and legal
9 status, which varies across countries. So our
10 results are not necessarily applicable to
11 countries with very different legal and
12 cultural attitudes to drugs. Right?

13 A Well, you know, it's nice to see a
14 discussion that includes such a statement.
15 But the fact is, is that Great Britain is a
16 member of international psychotropic treaty,
17 just like the United States, and is subject to
18 the same international conventions as the
19 United States for the control of drugs listed
20 as, you know, Schedule I in the United States,
21 Schedule A in Great Britain. And there is a
22 significant overlap in our western societies.
23 So it's -- it's doubtful that such a concern
24 would be of significant relevance as here in
25 the United States.

2 Q Okay. And the researchers also
3 noted there that a low score in their
4 assessment didn't mean that a drug wasn't
5 harmful. Correct?

6 A Absolutely, that's correct.
7 Absolutely, that's true.

8 Q All right. I have --

9 A Nobody should take that message
10 that a drug is safe. There's no drug that's
11 safe.

12 MS. MOORE: All right, thank you.

13 I don't have any more questions.

14 EXAMINATION BY MR. SCOLNICK:

15 Q Just a couple further questions,
16 Doctor.

17 The government discussed with you
18 a number of studies. It sounds like those
19 studies occurred between 2004 and 2010. Is
20 that right?

21 A I believe so. A number of them
22 were.

23 Q Well, we talked about Kish,
24 McCann, Jacobsen, Jager, Von Geusau?

25 A Yeah, yeah, that's right.

2 Q All of this information was
3 available before 2011. Right?

4 A That's correct.

5 Q And these aren't the only studies
6 in the field of MDMA cognitive research, are
7 they?

8 A No, there's thousands of papers on
9 MDMA.

10 Q And are there a number of studies
11 that agree with your findings?

12 A There are a number of studies that
13 agree with our findings. The work of Gill and
14 Magetty was published, I think, subsequent to
15 my work. And Dr. Michael Laverse from
16 Australia has published some evidence similar.
17 And there have been other groups as well that
18 have done some -- some overlap with the
19 results that we report, but none of them are
20 with the number of individuals or the control
21 for the compounding variable that I mentioned
22 quite like the work that was published in
23 2011, which I believe still should be
24 considered the standard reference by which we
25 should look at this question, although

2 controversial, of what happens when people who
3 abuse MDMA and their cognitive performance.

4 Q And with respect to the issue of
5 significant cognitive impairment, secondary to
6 MDMA use, what is your opinion and conclusions
7 of the vast majority of MDMA researchers?

8 A That there are some findings that
9 are -- that raises concern and warrant
10 continued investigation, as well as
11 surveillance of those who are MDMA users. But
12 it remains controversial to assert one
13 physician over the other as still enough basic
14 and clinical research to point to some
15 deference in performance which are not, right
16 now, found to be of significance but that's
17 still hurtful. It needs to be looked at.

18 But there is no data that is
19 supportive of identifying MDMA as being a
20 concerning drug to people's cognitive
21 functioning nor is there data to warrant at
22 this point the assertion that MDMA is more
23 dangerous than cocaine or that MDMA is even an
24 equivalent danger to MDMA. So we have a
25 tremendous amount of data showing that cocaine

2 is indeed more dangerous than MDMA.

3 I don't know any doctor that would
4 oppose that statement about MDMA versus
5 cocaine. Not a single physician could, have I
6 ever found, and I ask this a lot, that finds
7 cocaine safer than MDMA. It's just absurd to
8 ever proffer such a conclusion at this point
9 of what we know, both clinically and in
10 scientific literature. That is conclusive.

11 (Continued on the next page.)

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MR. SCOLNICK: Thank you, Doctor.
I have nothing further.

(Whereupon, matter concluded;
time noted: 12:06 p.m.)

DR. JOHN HALPERN, M.D.

Subscribed and sworn to before me
this _____ day of _____, 2014

NOTARY PUBLIC

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C E R T I F I C A T E

STATE OF NEW YORK)

:SS

COUNTY OF NEW YORK)

I, CHARISSE KITT, a Notary Public
for and within the State of New York, do
hereby certify:

That the witness whose examination
is hereinbefore set forth was duly sworn and
that such examination is a true record of the
testimony given by that witness.

I further certify that I am not
related to any of the parties to this action
by blood or by marriage and that I am in no
way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have
hereunto set my hand this 29th day of August,
2014.

CHARISSE KITT, CRI, CSR, RMR, FCRR

1	A	agree [7] 18/2 18/5 18/20 68/25 74/11 74/13 ahead [2] 4/18 64/21 al [2] 50/12 62/14 alcohol [24] 5/4 5/18 15/3 15/17 29/7 29/9 33/8 33/17 33/19 33/20 33/23 34/6 44/10 45/20 53/24 54/4 54/5 54/14 54/17 54/21 56/3 56/6 56/8 64/10 all [24] 5/5 5/22 14/15 14/22 15/19 20/23 31/14 37/7 39/9 40/3 41/6 42/10 43/19 47/7 53/21 53/22 54/17 65/22 66/20 70/3 72/4 73/8 73/12 74/2 allowing [1] 69/6 allows [1] 46/23 almost [4] 24/25 37/7 37/11 43/19 alone [1] 19/3 alongside [2] 47/18 47/24 already [1] 53/20 also [36] 5/8 5/11 6/8 14/3 14/5 14/7 16/4 16/24 18/16 20/8 22/2 22/17 22/22 23/3 23/15 23/16 23/18 24/4 25/3 27/25 31/8 33/17 33/18 40/20 46/7 56/4 56/9 60/16 61/25 62/24 63/18 64/23 66/6 68/15 69/18 73/2 alter [2] 63/3 69/15 alteration [2] 70/17 70/19 alterations [1] 27/24 although [1] 74/25 am [9] 5/3 5/8 6/11 6/24 7/21 11/13 61/24 78/14 78/16 AMERICA [2] 1/5 13/2 American [1] 54/12 Americans [1] 54/13 amino [1] 69/9 among [3] 29/16 31/4 61/3 amount [7] 7/24 20/15 20/20 20/22 26/22 39/7 75/25 Amsterdam [1] 13/24 Amsterdam's [1] 16/4 analysis [2] 7/19 40/19 and/or [1] 50/5 animal [2] 8/23 8/24 animals [1] 62/20 another [5] 14/2 24/13 40/11 43/6 49/7 answer [1] 36/16 antidepressants [1] 12/11 antitumor [1] 26/13 any [35] 13/15 14/12 15/22 16/9 19/12 25/17 27/10 28/7 28/15 29/3 30/25 33/16 34/11 34/11 36/19 36/20 41/12 42/12 45/10 47/6 47/14 48/6 49/11 52/5 52/8 53/10 54/18 57/20 64/2 64/21 65/10 65/11 73/13 76/3 78/15 anybody [1] 47/25 anything [4] 45/11 48/4 49/3 71/18 anywhere [1] 12/23 apart [2] 37/21 47/11 apparently [1] 24/14 appeared [1] 47/24 appears [1] 51/2 applicable [1] 72/10 applying [1] 36/11 appointment [1] 5/14 approved [5] 10/23 61/18 64/17 64/21 71/13 approximately [4] 6/23 60/3 62/11 63/13 are [95] area [2] 5/2 54/22 areas [1] 61/4 aren't [2] 69/24 74/5 argument [1] 67/10 around [5] 6/18 30/15 30/17 31/11 48/21 arteries [1] 27/16 article [10] 45/25 48/19 50/16 50/21 51/3 51/8 51/12 51/21 56/19 71/25 articles [2] 6/19 6/20
2	abuse [32] 5/4 5/7 5/18 6/10 6/14 15/4 15/10 15/12 16/23 17/20 19/14 19/23 21/5 23/3 23/4 23/7 28/16 28/23 31/25 32/6 33/10 37/4 40/12 40/18 41/15 44/19 45/22 52/10 62/24 67/21 68/21 75/3 abused [3] 12/5 56/2 56/7 abuser [1] 19/10 abusers [4] 22/16 24/20 26/16 41/17 abusing [3] 5/20 41/19 55/21 academic [1] 32/10 accept [1] 67/24 accepted [2] 17/10 49/18 access [1] 53/19 according [2] 30/13 68/5 accounted [1] 42/7 accurate [10] 6/22 10/24 10/25 28/11 29/18 29/19 39/5 39/14 62/8 63/20 accurately [1] 18/6 achieve [1] 62/21 acid [1] 69/9 across [3] 13/21 56/18 72/9 action [1] 78/15 actions [1] 69/10 activity [3] 10/14 13/11 56/4 actual [6] 36/8 47/10 60/12 65/14 65/20 68/19 actually [13] 9/19 30/11 32/21 32/22 36/7 44/17 44/25 51/2 58/23 58/24 61/18 62/21 64/11 acute [5] 20/13 21/8 63/2 63/5 68/6 addicted [3] 5/20 20/3 54/21 addiction [4] 12/16 21/22 45/21 46/2 addictive [7] 12/14 17/12 17/16 18/2 18/11 18/13 18/21 additional [3] 23/10 41/9 48/17 address [1] 49/25 addressed [2] 39/24 41/5 administered [1] 42/13 administration [1] 69/18 admission [1] 15/13 admissions [2] 32/16 32/18 admit [2] 15/11 56/13 admitted [1] 15/15 adults [3] 29/17 31/4 55/21 advanced [1] 10/5 affect [3] 19/19 19/19 22/10 affected [1] 72/8 affects [4] 5/15 8/19 18/17 68/6 affiliated [1] 71/8 after [7] 4/14 9/14 9/25 21/14 49/13 64/13 69/23 again [8] 3/3 16/6 20/20 21/24 32/20 38/13 61/14 66/24 against [1] 69/11 age [2] 40/7 56/3 agenda [1] 71/16 aggression [1] 28/23 aggressively [2] 54/25 55/15 ago [1] 26/8	
3		
4		
5		
6		
9		
:		
:SS [1] 78/5		

<p>A</p> <p>as [66] 3/11 3/13 4/21 4/24 5/8 5/10 5/18 7/2 12/19 12/21 13/24 14/15 15/6 16/3 16/3 17/9 18/17 18/18 19/11 23/17 24/5 25/4 27/8 29/24 29/24 32/9 32/9 33/21 34/6 34/6 35/7 35/11 37/10 37/10 37/24 38/21 38/21 41/4 41/4 41/20 41/24 42/18 47/4 51/12 55/16 56/6 56/13 58/4 58/4 63/7 64/2 64/3 67/11 68/12 68/14 68/17 71/8 71/9 72/18 72/20 72/24 74/17 75/10 75/10 75/13 75/19</p> <p>ask [2] 38/16 76/6</p> <p>asking [2] 14/6 15/4</p> <p>assert [2] 33/12 75/12</p> <p>asserting [1] 65/13</p> <p>assertion [1] 75/22</p> <p>assessment [3] 13/22 30/5 73/4</p> <p>associate [1] 5/12</p> <p>associated [18] 22/14 22/19 24/16 25/18 26/24 27/11 28/7 28/14 28/24 29/9 33/11 36/2 36/8 39/19 39/20 43/5 43/9 66/22</p> <p>associative [1] 66/22</p> <p>assumed [1] 38/10</p> <p>assuming [1] 20/2</p> <p>assuring [1] 67/18</p> <p>attack [2] 19/22 68/15</p> <p>attacking [1] 44/21</p> <p>attacks [2] 27/18 69/23</p> <p>attempt [2] 9/2 34/14</p> <p>attempted [2] 38/9 67/11</p> <p>attempts [1] 34/20</p> <p>attend [1] 4/6</p> <p>attenuated [1] 21/10</p> <p>attitudes [1] 72/12</p> <p>ATTORNEYS [3] 2/5 2/6 2/12</p> <p>August [2] 1/13 78/19</p> <p>Australia [1] 74/16</p> <p>authors [4] 46/17 71/3 71/7 72/6</p> <p>availability [2] 34/7 72/8</p> <p>available [6] 11/2 16/16 23/10 30/21 34/12 74/3</p> <p>average [2] 60/4 60/8</p> <p>Award [1] 4/19</p> <p>awarded [1] 4/15</p> <p>aware [27] 6/8 13/15 27/21 28/15 52/8 59/25 60/24 61/5 61/19 61/24 62/12 63/11 63/17 63/18 64/5 65/16 66/5 66/20 68/5 69/8 69/14 70/7 71/3 71/11 71/12 71/20 71/25</p> <p>away [1] 53/2</p>	<p>74/17</p> <p>before [18] 1/21 5/21 7/10 7/16 8/4 31/17 35/16 41/12 46/5 47/4 49/9 49/16 50/7 51/18 56/12 59/5 74/3 77/12</p> <p>begin [1] 69/16</p> <p>beginning [1] 71/2</p> <p>behavior [5] 20/17 28/14 28/17 28/20 36/3</p> <p>being [8] 19/9 22/16 27/22 27/23 37/11 67/11 67/17 75/19</p> <p>belief [1] 10/16</p> <p>believe [30] 8/9 10/20 11/4 11/11 13/24 14/4 16/3 16/4 17/24 23/8 27/25 30/3 30/7 30/13 30/23 31/18 32/19 33/19 34/18 35/18 37/12 45/19 48/20 49/6 51/10 54/25 58/19 60/21 73/21 74/23</p> <p>believed [2] 9/11 48/4</p> <p>believes [1] 28/21</p> <p>below [1] 47/13</p> <p>benefits [1] 64/23</p> <p>best [5] 13/6 38/21 39/4 39/16 71/2</p> <p>bet [1] 65/6</p> <p>better [6] 8/21 8/22 9/2 9/4 40/9 40/10</p> <p>between [13] 6/19 8/17 15/23 21/22 28/16 29/6 30/11 30/12 33/2 52/20 61/21 63/15 73/19</p> <p>binding [7] 9/13 9/18 10/9 61/14 61/21 61/25 63/16</p> <p>bit [6] 19/18 30/17 31/19 32/23 36/17 37/15</p> <p>blood [3] 33/24 68/13 78/16</p> <p>bloodstream [1] 34/8</p> <p>body [1] 8/19</p> <p>book [1] 6/20</p> <p>borne [1] 26/4</p> <p>Boston [1] 4/25</p> <p>both [13] 28/8 40/19 45/18 48/13 52/22 52/22 58/3 59/11 59/12 59/14 59/16 59/18 76/9</p> <p>brain [26] 9/8 9/25 10/8 10/14 10/22 13/11 35/13 35/23 35/23 41/11 41/16 44/17 48/8 51/24 54/6 61/9 63/2 63/3 63/4 63/7 64/11 65/3 68/17 69/10 70/12 70/14</p> <p>brains [1] 69/23</p> <p>break [1] 37/15</p> <p>briefly [2] 3/20 70/24</p> <p>bringing [1] 39/21</p> <p>Britain [2] 72/15 72/21</p> <p>broad [1] 7/9</p> <p>broaden [1] 36/17</p> <p>broadly [2] 8/20 59/8</p> <p>broken [1] 56/5</p> <p>Brooklyn [3] 1/20 2/8 2/14</p> <p>builds [1] 21/8</p> <p>Bureau [1] 22/3</p> <p>burning [2] 25/14 25/21</p> <p>busy [1] 3/19</p>	<p>case [2] 54/10 54/24</p> <p>cause [7] 9/12 27/16 27/24 53/18 53/22 54/2 64/25</p> <p>caused [1] 13/14</p> <p>causes [7] 19/21 24/9 36/20 53/25 54/5 68/15 70/14</p> <p>causing [1] 12/16</p> <p>cell [1] 36/8</p> <p>cells [1] 64/11</p> <p>cerebral [1] 62/17</p> <p>certain [2] 24/24 60/14</p> <p>certainly [2] 19/19 60/18</p> <p>certify [2] 78/9 78/14</p> <p>change [2] 35/23 70/12</p> <p>changed [2] 8/19 11/18</p> <p>changes [8] 9/24 11/20 25/22 35/12 51/24 64/15 64/18 69/16</p> <p>chapters [2] 6/20 58/24</p> <p>characterized [1] 42/18</p> <p>charge [1] 4/25</p> <p>CHARISSE [3] 1/21 78/7 78/23</p> <p>CHASE [2] 2/15 3/3</p> <p>cheaper [1] 23/25</p> <p>chemistry [1] 63/4</p> <p>chemotherapy [1] 65/4</p> <p>cherrypick [3] 47/9 63/24 70/12</p> <p>cherrypicking [1] 50/2</p> <p>children [1] 55/2</p> <p>CHIN [1] 1/10</p> <p>CHONG [1] 1/10</p> <p>choose [1] 47/8</p> <p>chronically [1] 27/23</p> <p>church [1] 54/12</p> <p>cigarette [2] 26/9 26/19</p> <p>cigarettes [1] 27/3</p> <p>cite [2] 47/9 47/25</p> <p>cited [3] 11/17 61/10 66/18</p> <p>citing [1] 70/15</p> <p>claimed [1] 53/18</p> <p>claiming [1] 10/20</p> <p>clarify [2] 54/2 57/4</p> <p>clear [2] 34/16 67/10</p> <p>clearly [1] 46/15</p> <p>clinical [14] 5/6 8/11 11/24 19/7 19/9 41/12 56/17 61/16 62/7 65/12 68/7 68/10 71/9 75/14</p> <p>clinically [7] 45/12 52/9 52/12 52/14 53/8 70/3 76/9</p> <p>clinics [1] 21/25</p> <p>Clonidine [1] 53/21</p> <p>close [2] 12/20 31/11</p> <p>closely [1] 62/4</p> <p>closer [1] 30/18</p> <p>cocaine [80] 8/9 8/10 8/13 12/17 12/21 13/3 14/16 14/24 15/5 15/8 15/9 15/10 15/20 17/3 17/6 17/11 17/19 17/22 18/10 18/10 19/14 19/18 20/3 20/8 21/22 22/8 22/14 22/16 22/18 23/21 23/22 23/23 23/24 24/8 24/9 24/13 24/14 24/16 24/20 27/8 27/12 27/15 28/16 28/18 28/23 29/4 32/17 32/22 33/10 33/13 34/24 35/8 58/20 59/4 59/6 59/6 59/7 59/8 59/10 59/10 59/16 59/17 59/17 64/3 65/15 68/6 69/3 69/17 69/18 69/21 69/22 69/25 70/4 70/6 70/8 70/20 75/23 75/25 76/5 76/7</p> <p>cognitive [21] 18/24 36/18 36/20 38/13 38/19 40/15 42/11 44/6 45/8 48/10 52/7 54/16 54/19 65/2 65/9 66/8 68/15 74/6 75/3 75/5 75/20</p> <p>colleague [2] 10/19 13/25</p> <p>colleagues [2] 15/2 29/24</p> <p>collects [1] 32/3</p> <p>college [2] 40/7 48/13</p> <p>college-age [1] 40/7</p> <p>collusion [1] 22/20</p> <p>combine [1] 26/15</p>
<p>B</p> <p>B1 [1] 7/5</p> <p>back [3] 12/8 18/9 29/11</p> <p>based [6] 11/15 11/20 28/8 32/24 45/3 49/11</p> <p>basic [3] 11/24 33/22 75/13</p> <p>basically [4] 35/8 38/17 44/21 47/13</p> <p>basis [3] 5/23 15/10 70/5</p> <p>be [53] 6/4 9/12 9/13 12/2 12/4 12/10 12/11 13/6 14/19 14/23 25/22 26/14 28/8 28/9 28/9 28/25 34/6 36/2 36/6 36/16 37/24 38/10 38/24 39/5 40/11 41/13 43/18 43/20 44/3 48/4 50/3 52/22 55/3 56/4 56/9 57/9 58/19 63/19 64/13 64/24 65/12 66/3 67/18 67/24 67/25 69/5 70/2 70/10 70/21 72/24 74/23 75/16 75/17</p> <p>because [27] 15/15 19/13 20/12 21/7 22/7 24/17 26/2 26/16 27/5 27/14 33/22 37/15 38/9 39/3 39/4 40/3 40/9 40/10 41/14 46/21 50/23 55/16 61/13 62/20 64/22 70/11 71/7</p> <p>become [2] 20/16 55/8</p> <p>been [29] 3/11 5/20 5/24 6/12 8/21 10/9 10/23 11/22 11/24 12/13 13/18 16/10 20/2 30/2 41/21 48/6 48/12 48/17 49/18 51/17 51/23 53/17 54/13 54/15 56/10 64/20 66/14 70/8</p>	<p>C</p> <p>Cadman [2] 1/20 2/7</p> <p>calculated [1] 34/21</p> <p>call [2] 48/3 64/11</p> <p>called [2] 3/11 11/10</p> <p>can [33] 3/7 3/23 13/7 13/10 15/18 18/4 25/22 27/16 28/19 28/25 34/6 34/17 36/2 36/23 37/24 38/21 40/18 41/22 43/16 45/4 46/15 52/15 53/22 53/25 60/10 61/12 64/23 65/12 66/3 67/23 68/18 69/16 70/2</p> <p>can't [6] 15/14 47/7 47/8 47/9 70/12 71/15</p> <p>cancer [3] 26/6 26/12 65/3</p> <p>cannabis [4] 26/3 26/12 26/16 26/16</p> <p>capsule [1] 25/5</p> <p>capturing [1] 43/20</p> <p>cards [1] 44/22</p> <p>care [1] 68/18</p> <p>carrying [1] 68/16</p>	

<p>C</p> <p>combined [1] 66/9 Commission [4] 11/4 11/9 11/12 29/12 Commission's [2] 7/19 69/3 common [3] 29/9 55/25 56/9 communities [2] 13/2 22/10 community [7] 9/22 10/17 17/11 20/7 39/14 39/21 49/19 comparative [4] 9/19 15/23 17/2 40/6 compare [2] 8/24 32/15 compared [4] 13/16 15/17 42/13 66/18 comparing [1] 54/4 comparison [4] 54/11 54/12 58/20 58/25 competent [1] 47/15 completed [2] 36/25 37/12 completely [1] 49/24 completing [1] 4/14 completion [1] 6/5 complicated [1] 19/2 compound [6] 37/17 41/9 41/13 42/3 43/18 43/24 compounded [1] 38/3 compounding [1] 74/21 compounds [12] 9/2 25/13 37/5 37/16 38/2 38/4 38/17 39/20 41/2 42/7 65/23 66/25 comprehension [1] 48/8 comprehensive [1] 47/23 comprises [1] 5/5 concern [10] 12/14 25/24 29/15 29/17 29/19 43/4 43/8 55/4 72/23 75/9 concerned [3] 16/7 53/23 54/24 concerning [5] 45/11 64/4 64/4 67/4 75/20 concerns [3] 11/17 11/21 26/14 conclude [1] 45/7 concluded [2] 14/22 77/4 conclusion [5] 11/6 11/21 18/3 63/25 76/8 conclusions [3] 45/4 51/20 75/6 conclusive [1] 76/10 conducted [2] 7/20 14/10 confidence [4] 9/3 37/25 41/25 67/2 confirm [3] 16/6 40/19 40/21 confirmed [1] 52/6 conflict [1] 71/4 consensus [5] 14/12 17/2 17/5 17/6 20/7 consent [1] 64/24 consequence [1] 67/4 consequences [2] 18/19 54/10 consider [1] 43/25 consideration [1] 14/14 considered [8] 11/5 11/9 11/12 15/7 29/13 64/17 64/20 74/24 consistent [2] 29/3 62/23 constrictive [1] 27/15 construct [1] 9/3 consume [1] 21/13 consumed [1] 27/6 consumption [2] 25/9 56/3 contact [1] 5/25 continue [5] 17/21 20/14 20/17 66/15 69/7 continued [3] 69/17 75/10 76/11 control [9] 9/2 39/8 40/2 40/11 41/2 42/2 65/23 72/19 74/20 controlled [3] 13/9 13/17 14/11 controversial [3] 67/7 75/2 75/12 controversy [1] 67/8 conventions [1] 72/18 copy [1] 50/12 correct [26] 6/16 6/23 7/13 10/2 11/19 11/23 16/19 17/13 20/4 39/2 44/7 46/2 46/3 46/25 47/5 49/17 51/25 52/2 58/2 58/11 58/12 59/18 59/24 73/5 73/6 74/4 CORRECTION [2] 79/4 80/4</p>	<p>correctly [4] 9/21 28/7 30/10 44/4 correlate [1] 66/8 correlation [1] 61/21 cortex [2] 61/3 62/17 could [12] 8/13 20/11 32/15 38/24 42/8 52/11 52/22 53/15 58/13 58/15 62/25 76/5 couldn't [1] 59/13 Council [1] 58/14 counselor [1] 5/19 counter [1] 53/11 counting [1] 44/22 countries [2] 72/9 72/11 country [4] 25/16 27/9 29/22 58/15 COUNTY [1] 78/6 couple [6] 23/17 31/18 42/9 43/14 57/4 73/15 course [6] 12/17 22/25 24/12 46/9 71/23 71/23 COURT [5] 1/2 1/19 30/21 46/5 47/4 cover [1] 3/18 coverage [2] 4/25 5/3 Cowan [1] 62/14 CR [1] 1/8 crack [4] 23/25 59/7 59/11 59/17 crash [1] 20/19 craving [1] 20/13 create [1] 42/16 CRI [2] 1/21 78/23 crime [3] 12/16 21/23 29/10 crimes [1] 22/7 criminal [2] 22/25 23/5 criteria [2] 14/7 20/23 criticizing [1] 50/17 critique [1] 49/23 critiquing [1] 50/17 crosses [1] 58/23 CSR [2] 1/22 78/23 cultural [1] 72/12 culture [2] 23/8 55/10 curious [1] 43/23 current [3] 7/23 11/5 17/15 CV [1] 6/25</p>	<p>54/3 decided [1] 46/17 declarant [1] 61/15 decline [2] 30/6 45/8 declined [1] 30/11 decrease [5] 9/12 37/24 52/25 53/9 53/13 decreased [3] 9/14 55/19 61/6 DEFENDANT [2] 1/11 2/12 Defendant's [6] 7/5 50/10 50/14 51/12 51/19 56/24 DEFENDERS [1] 2/11 Defense [2] 7/2 56/13 deference [3] 19/13 68/16 75/15 deficit [1] 61/22 deficits [3] 53/19 53/23 64/6 defined [1] 35/20 definitely [1] 9/4 definition [5] 35/18 36/10 36/11 36/12 70/22 demonstrated [1] 65/17 dendrites [5] 70/9 70/13 70/18 70/19 70/21 department [5] 30/4 31/2 57/16 57/20 58/4 dependent [3] 18/16 20/16 20/24 dependents [2] 17/23 45/20 depletion [1] 62/15 DEPOSITION [1] 1/17 depravation [1] 40/2 depressed [1] 12/10 deprivation [1] 45/7 deprived [1] 40/5 describe [1] 21/13 described [5] 11/16 29/4 39/16 59/3 68/14 describing [1] 64/19 design [1] 37/23 designed [4] 25/20 37/8 37/20 44/17 desired [1] 21/14 destructive [1] 21/2 detail [2] 8/16 50/8 detailed [1] 49/22 determine [5] 8/13 33/16 34/11 34/12 38/19 detriment [1] 64/12 detriments [3] 61/25 63/6 63/6 developing [1] 71/12 did [16] 4/6 10/6 15/16 26/11 42/4 43/10 44/5 44/11 44/13 44/24 45/6 45/10 45/11 46/12 58/24 66/12 didn't [3] 43/15 68/8 73/4 differ [1] 44/14 difference [3] 33/2 42/11 52/20 differences [1] 42/21 different [6] 6/18 12/2 23/3 45/2 54/8 72/11 differentiate [1] 35/22 difficult [2] 38/24 65/25 direct [2] 18/16 71/16 directly [1] 68/20 director [4] 4/24 5/3 5/8 71/8 discuss [1] 42/8 discussed [4] 56/14 57/5 72/2 73/17 discussing [2] 59/6 59/7 discussion [1] 72/14 discussions [1] 59/8 disease [1] 12/12 distributing [1] 23/2 distribution [4] 22/8 22/17 22/20 22/25 DISTRICT [4] 1/2 1/3 1/19 1/19 division [2] 5/4 15/3 do [39] 8/9 15/22 17/20 17/21 21/4 27/9 35/18 36/16 38/11 38/18 38/24 39/8 39/16 40/6 40/14 40/18 41/15 41/25 42/15 42/21 47/15 51/20 51/22 52/11 53/22 55/4 58/12 58/13 58/21 58/24 60/8 61/17 62/23 64/9 64/14 66/12 66/15 72/4 78/8 doctor [7] 4/2 14/9 44/5 48/23 73/16 76/3 77/2</p>
	<p>D</p> <p>daily [3] 5/23 15/10 54/13 damage [10] 19/6 28/4 28/7 35/12 35/23 53/3 54/6 54/17 68/3 70/14 damages [2] 15/9 70/4 damaging [2] 37/5 54/19 dance [3] 40/4 42/10 55/7 danger [3] 65/14 67/11 75/24 dangerous [22] 8/12 12/25 14/16 15/5 17/7 18/23 18/25 22/9 22/12 22/13 24/14 25/25 26/23 32/8 35/2 63/21 64/3 67/25 69/5 69/25 75/23 76/2 dangers [1] 14/14 data [46] 9/22 11/3 12/19 13/5 14/17 16/16 28/2 30/5 30/7 30/8 30/20 30/23 31/5 31/9 31/15 31/23 32/5 32/14 32/15 32/16 32/20 32/25 33/5 33/6 34/19 38/3 38/3 42/9 42/16 43/18 44/2 46/18 48/7 48/20 54/18 55/18 57/12 58/14 58/21 58/23 60/11 60/12 62/9 75/18 75/21 75/25 database [4] 32/2 32/3 34/20 34/22 date [1] 16/8 David [1] 13/20 DAWN [2] 32/2 32/20 day [4] 21/9 27/24 77/13 78/19 days [4] 20/18 20/21 21/7 40/17 deal [1] 15/9 dealers [1] 55/12 dealing [1] 55/20 dealt [2] 16/22 19/25 death [7] 27/16 36/7 36/13 36/15 53/24 53/25</p>	

<p>D</p> <p>doctors [1] 16/24</p> <p>document [2] 11/10 31/2</p> <p>does [10] 19/5 19/6 35/4 36/13 36/16 37/18 54/2 63/25 64/2 64/10</p> <p>doesn't [4] 58/22 62/22 64/9 65/10</p> <p>doing [9] 20/20 26/20 30/2 38/5 39/14 39/15 40/8 68/2 68/4</p> <p>don't [7] 19/16 30/23 38/5 53/25 67/21 73/13 76/3</p> <p>done [5] 29/21 36/19 45/2 54/8 74/18</p> <p>dopaminergic [2] 69/12 69/13</p> <p>dose [5] 34/3 62/13 62/15 62/21 65/4</p> <p>doses [2] 62/19 63/13</p> <p>dosing [1] 8/23</p> <p>doubt [2] 19/14 67/5</p> <p>doubtful [1] 72/23</p> <p>down [5] 30/19 31/19 31/20 37/15 41/22</p> <p>downward [1] 31/17</p> <p>DR [7] 1/18 3/3 3/10 7/7 60/16 63/25 77/10</p> <p>Dr. [25] 3/17 10/4 10/10 10/12 10/25 11/2 13/20 13/24 14/2 16/3 16/4 16/5 16/5 17/24 18/5 18/8 26/5 47/22 47/22 47/22 49/23 51/5 63/18 63/23 74/15</p> <p>Dr. Amsterdam [1] 13/24</p> <p>Dr. Amsterdam's [1] 16/4</p> <p>Dr. David [1] 13/20</p> <p>Dr. Halpern [1] 3/17</p> <p>Dr. Kish [4] 10/4 10/25 47/22 63/18</p> <p>Dr. Kish's [2] 10/10 10/12</p> <p>Dr. McCann [1] 11/2</p> <p>Dr. Michael [1] 74/15</p> <p>Dr. Morgan [2] 14/2 16/3</p> <p>Dr. Nut's [2] 16/5 16/5</p> <p>Dr. Parrot [4] 17/24 18/5 47/22 63/23</p> <p>Dr. Parrot's [3] 18/8 49/23 51/5</p> <p>Dr. Rogers [1] 47/22</p> <p>Dr. Tishkent [1] 26/5</p> <p>drawn [1] 11/6</p> <p>drinkers [1] 54/14</p> <p>drug [63] 5/4 6/2 7/13 7/19 8/5 15/4 16/23 18/14 18/17 19/3 19/10 20/12 20/22 20/25 21/13 23/7 23/18 24/22 30/2 30/4 30/14 31/6 31/25 32/6 32/8 32/13 33/10 34/19 36/3 37/4 39/13 39/20 40/14 41/10 41/11 41/17 41/19 44/19 45/20 48/14 55/9 55/12 57/15 57/20 57/25 58/9 58/10 62/24 63/22 64/17 64/21 64/23 65/8 65/10 65/24 67/15 67/15 68/20 69/4 73/4 73/10 73/10 75/20</p> <p>drugs [31] 5/20 8/8 13/8 13/21 13/23 14/7 18/2 19/23 28/15 34/10 34/13 34/15 40/12 40/18 40/19 40/21 41/15 53/10 53/12 53/15 53/21 56/2 57/23 61/17 64/25 67/21 67/24 68/2 72/7 72/12 72/19</p> <p>due [1] 43/5</p> <p>duly [2] 3/11 78/11</p> <p>during [4] 59/8 63/4 63/4 65/18</p> <p>dying [1] 65/2</p>	<p>editorial [1] 50/25</p> <p>effect [4] 20/8 21/10 36/14 53/12</p> <p>effects [6] 21/14 29/2 38/19 44/7 48/10 62/13</p> <p>egos [1] 28/21</p> <p>eighth [1] 31/7</p> <p>eighth graders [1] 31/7</p> <p>either [1] 53/11</p> <p>electronic [1] 55/7</p> <p>elements [2] 5/5 41/6</p> <p>elicit [2] 56/4 57/20</p> <p>elicited [1] 56/8</p> <p>else [1] 52/18</p> <p>emergency [21] 12/19 13/6 19/24 31/22 31/23 32/4 32/12 32/16 32/17 32/21 33/6 33/11 57/6 57/9 57/15 57/20 58/4 58/8 58/11 58/16 58/18</p> <p>empirical [1] 51/16</p> <p>employment [1] 19/11</p> <p>encountered [1] 5/19</p> <p>end [4] 18/2 18/18 58/10 68/22</p> <p>enema [1] 23/17</p> <p>England [1] 13/20</p> <p>enjoy [1] 18/4</p> <p>enough [2] 61/15 75/13</p> <p>ensure [1] 40/16</p> <p>enterprise [1] 23/6</p> <p>enterprises [1] 23/2</p> <p>entertainment [1] 55/14</p> <p>entice [1] 55/11</p> <p>entitled [2] 51/13 56/15</p> <p>equivalent [1] 75/24</p> <p>ER [2] 33/15 34/10</p> <p>ERRATA [2] 79/2 80/2</p> <p>especially [2] 51/4 60/19</p> <p>ESQ [2] 2/9 2/15</p> <p>essentially [1] 42/20</p> <p>estimate [1] 58/17</p> <p>estimated [1] 58/14</p> <p>et [2] 50/11 62/14</p> <p>ethical [1] 39/15</p> <p>evaluate [3] 38/12 47/12 48/2</p> <p>evaluating [2] 41/21 44/17</p> <p>even [16] 11/25 15/14 20/25 21/2 23/10 24/25 25/3 26/21 34/4 38/4 43/25 63/22 63/24 65/8 69/25 75/23</p> <p>event [2] 9/16 15/13</p> <p>ever [4] 37/2 68/25 76/6 76/8</p> <p>every [3] 15/3 27/23 59/15</p> <p>everyday [1] 53/4</p> <p>evidence [5] 9/15 27/22 35/25 50/9 74/16</p> <p>exact [1] 6/4</p> <p>exactly [2] 14/25 15/6</p> <p>exaggerates [1] 50/18</p> <p>examination [5] 3/16 56/25 73/14 78/10 78/12</p> <p>examined [2] 3/12 22/6</p> <p>examining [1] 63/12</p> <p>example [15] 9/7 9/10 12/17 17/9 18/20 24/11 24/13 26/8 33/5 34/14 35/23 53/17 66/10 70/10 70/21</p> <p>excellent [1] 29/21</p> <p>excessive [1] 29/7</p> <p>excitatory [1] 69/10</p> <p>exclude [1] 41/2</p> <p>exclusive [2] 44/25 59/10</p> <p>excuse [2] 6/25 69/11</p> <p>executive [2] 66/9 71/8</p> <p>exhaustive [2] 42/12 54/15</p> <p>exhibit [10] 7/2 7/5 46/5 47/4 50/10 50/14 51/12 51/19 56/13 56/24</p> <p>exhibited [1] 17/18</p> <p>exist [3] 34/21 37/6 66/11</p> <p>existed [1] 37/10</p> <p>expanded [1] 43/14</p> <p>expands [2] 20/21 20/22</p>	<p>expect [4] 24/17 24/25 56/9 66/3</p> <p>expected [1] 56/4</p> <p>experience [10] 5/17 16/22 18/12 20/6 23/12 29/6 34/2 34/3 55/20 55/22</p> <p>expert [3] 8/11 26/5 47/14</p> <p>experts [1] 56/18</p> <p>explain [4] 20/11 37/17 52/11 53/15</p> <p>explained [1] 46/14</p> <p>exploding [1] 29/16</p> <p>exposed [1] 41/21</p> <p>exposure [7] 26/21 28/2 33/23 40/10 44/9 63/2 64/13</p> <p>expressed [1] 29/15</p> <p>expression [2] 70/17 70/20</p> <p>extending [1] 64/12</p> <p>extensive [1] 54/15</p> <p>extrapolate [2] 45/4 66/2</p> <p>extreme [1] 26/13</p> <p>extremely [2] 15/13 29/8</p>
<p>E</p> <p>E.D [1] 58/5</p> <p>E.R [1] 57/25</p> <p>each [3] 14/19 19/3 57/22</p> <p>earlier [3] 9/3 31/21 55/17</p> <p>early [2] 16/10 29/17</p> <p>East [2] 1/20 2/7</p> <p>EASTERN [2] 1/3 1/19</p> <p>eat [1] 25/10</p> <p>ecstasy [13] 9/14 30/11 31/15 31/16 40/9 41/18 41/20 41/22 41/23 44/25 48/16 51/15 52/7</p> <p>editor [2] 6/21 50/25</p>	<p>F</p> <p>fact [12] 21/12 26/12 30/3 33/8 35/5 43/7 47/6 52/16 54/24 61/14 67/7 72/15</p> <p>factor [3] 34/24 43/6 58/15</p> <p>factors [3] 19/3 32/3 39/9</p> <p>fail [2] 47/12 47/12</p> <p>failure [2] 40/14 49/25</p> <p>failures [1] 37/9</p> <p>fair [5] 5/24 14/23 24/21 38/25 46/24</p> <p>fairly [2] 45/6 60/14</p> <p>familiar [7] 7/12 7/18 7/22 11/10 46/21 48/23 50/20</p> <p>family [2] 20/9 23/11</p> <p>far [1] 41/4</p> <p>fashion [3] 17/20 27/13 44/22</p> <p>fast [1] 20/13</p> <p>FCRR [2] 1/22 78/23</p> <p>FDA [3] 64/16 64/20 71/13</p> <p>fears [4] 11/17 11/21 12/4 12/8</p> <p>feature [2] 12/22 15/12</p> <p>FEDERAL [2] 2/11 22/3</p> <p>fellow [1] 4/20</p> <p>fellowships [1] 4/16</p> <p>few [7] 3/23 6/7 16/13 18/9 52/17 52/17 53/5 46/22 48/25 52/4 74/6</p> <p>final [1] 22/2</p> <p>find [5] 10/6 42/21 43/21 45/10 45/11</p> <p>finder [1] 47/7</p> <p>finding [6] 43/4 43/15 52/24 60/17 62/22 67/3</p> <p>findings [18] 11/15 37/25 42/8 43/17 44/11 44/13 47/11 50/19 52/6 53/8 63/17 63/23 65/11 66/4 66/16 74/11 74/13 75/8</p> <p>finds [2] 43/13 76/6</p> <p>fine [2] 16/7 60/20</p> <p>finger [3] 42/23 44/12 58/25</p> <p>finish [1] 56/12</p> <p>first [5] 17/9 43/7 44/13 44/15 45/19</p> <p>Fisk [1] 50/11</p> <p>five [2] 65/4 65/5</p> <p>fixing [1] 37/9</p> <p>flags [1] 63/21</p> <p>flexibility [1] 66/8</p> <p>Floor [1] 2/13</p> <p>FMRI [1] 66/21</p> <p>focuses [1] 31/6</p> <p>follow [3] 48/14 54/11 70/16</p> <p>following [1] 69/17</p> <p>follows [1] 3/13</p> <p>forgive [1] 64/6</p> <p>forgot [1] 56/20</p> <p>form [2] 24/23 64/24</p> <p>forth [2] 46/4 78/11</p>	

<p>F</p> <p>fortunately [2] 44/2 64/9 forward [1] 48/22 found [15] 10/13 42/11 43/8 51/24 60/25 61/7 61/15 61/20 62/14 63/14 66/13 66/21 69/15 75/16 76/6 free [1] 40/9 freebase [1] 23/25 frequently [1] 50/18 friends [1] 23/10 fully [1] 49/25 function [9] 18/24 43/9 43/18 54/20 63/3 65/2 65/18 65/19 66/9 functional [4] 36/2 45/13 54/10 63/8 functionality [1] 25/23 functionally [1] 52/23 functioning [6] 19/6 38/20 45/9 67/5 69/24 75/21 funded [3] 24/7 37/3 66/12 funding [3] 4/22 38/11 66/15 further [3] 73/15 77/3 78/14 Future [2] 29/23 31/5</p>	<p>HALPERN [7] 1/18 3/3 3/10 3/14 3/17 7/7 77/10 hand [1] 78/19 happened [1] 49/21 happens [3] 62/25 63/7 75/2 hard [3] 6/4 33/12 35/22 harm [5] 13/14 13/23 34/13 56/15 66/13 harmful [6] 8/5 8/10 14/7 14/24 59/16 73/5 harming [1] 68/22 harms [7] 13/16 13/22 14/11 15/23 17/2 18/13 72/7 Harvard [5] 4/12 4/16 4/20 5/12 5/14 has [33] 8/18 11/18 11/23 19/3 20/8 20/13 25/23 26/4 26/9 26/13 29/21 30/11 31/15 31/16 31/17 31/20 32/8 46/4 47/7 48/12 48/17 49/3 49/18 49/21 51/17 53/17 54/15 55/7 55/8 55/18 67/8 70/8 74/16 hasn't [2] 40/16 41/19 hate [1] 63/18 have [76] 3/17 4/23 5/13 5/19 5/20 7/17 8/22 11/22 12/13 12/23 13/16 15/14 16/9 16/13 20/2 21/4 21/10 21/20 21/21 22/2 22/6 32/11 34/2 34/5 35/15 36/13 36/18 38/9 39/5 40/25 41/8 41/17 41/23 41/24 41/25 42/17 42/19 43/16 46/7 46/10 48/6 49/10 51/23 51/24 52/6 52/24 53/5 53/12 55/17 55/22 56/2 56/5 58/21 58/23 60/2 60/8 61/6 64/19 64/22 65/10 65/10 66/14 67/2 67/3 67/14 67/19 67/19 67/23 73/8 73/13 74/17 74/18 75/24 76/5 77/3 78/18 haven't [1] 40/17 having [11] 3/11 12/5 16/22 20/3 21/14 27/17 32/8 43/22 54/8 65/8 68/15 he [3] 49/3 49/5 50/3 health [13] 5/7 11/25 12/3 12/6 13/5 18/19 19/12 19/20 25/17 27/11 65/15 67/3 69/5 hear [2] 59/13 68/8 heard [1] 35/15 hearing [5] 7/2 16/17 16/20 30/22 30/24 heart [6] 19/21 27/17 27/25 28/7 68/15 69/23 heat [1] 9/2 heated [1] 25/12 heating [1] 25/21 heavy [5] 23/18 42/19 43/3 54/13 60/19 held [1] 1/18 here [5] 3/4 16/8 51/8 53/7 72/24 hereby [1] 78/9 hereinbefore [1] 78/11 hereunto [1] 78/19 heroin [1] 24/6 HIAA [1] 62/16 high [1] 45/6 higher [4] 16/2 24/15 28/24 34/25 highly [5] 18/21 18/21 19/15 37/6 65/3 him [2] 49/2 49/24 hippocampus [3] 61/3 62/17 65/18 his [6] 26/7 26/10 50/4 63/17 63/19 63/22 histories [1] 40/21 history [1] 22/19 HIV [2] 24/12 24/15 hold [2] 26/17 43/15 home [1] 67/6 honestly [1] 66/16 Hospital [1] 5/5 hospitals [2] 4/25 5/18 house [1] 22/4 Household [2] 29/25 30/14 how [23] 8/18 9/6 15/16 21/15 22/9 23/12 23/21 24/9 24/14 33/16 37/16 39/9 41/11 41/13 41/24 44/11 44/13 49/18 53/19 55/6 58/17 69/20 69/25 However [1] 23/15 human [5] 8/23 8/25 49/21 51/14 62/20 human/animal [1] 8/23</p>	<p>humans [6] 8/22 28/5 28/10 62/4 62/23 64/16 hundred [3] 16/13 42/10 43/14 hurtful [1] 75/17 hurting [1] 21/3 hypothesized [1] 32/10</p> <p>I</p> <p>I'd [5] 7/7 17/8 33/12 35/10 51/11 I'll [1] 38/16 I'm [34] 3/22 6/6 8/2 16/7 20/2 21/25 22/15 23/5 24/24 27/12 27/21 31/8 48/9 50/8 50/22 52/8 56/20 59/13 60/11 60/14 60/15 60/16 60/21 61/5 63/17 63/17 64/7 65/21 66/3 68/11 69/11 71/11 71/16 71/18 I've [4] 23/17 32/14 36/25 50/12 idea [1] 55/3 identified [3] 43/6 48/15 64/6 identifies [1] 52/20 identify [1] 41/23 identifying [1] 75/19 ill [1] 35/20 ill-defined [1] 35/20 illegally [1] 22/18 illness [1] 19/5 imaging [4] 41/11 41/16 48/8 61/6 impact [7] 18/24 32/9 36/2 38/13 41/15 45/13 65/9 impacts [2] 9/6 19/15 impairment [5] 36/18 36/21 52/7 52/9 75/5 importance [2] 44/3 61/16 important [7] 10/4 23/9 26/3 33/21 35/24 36/5 67/13 importantly [2] 38/12 61/7 impossible [2] 37/22 38/10 impulsive [1] 44/20 impulsivity [3] 42/22 43/8 44/12 inadequate [4] 40/2 40/11 40/12 43/20 INC [1] 2/11 incarcerated [1] 22/7 incentivized [1] 65/24 include [2] 33/18 55/10 included [1] 59/12 includes [1] 72/14 including [5] 26/25 44/10 59/11 64/6 67/21 increase [2] 34/7 70/9 increased [3] 55/19 68/13 70/20 increases [1] 33/24 indeed [1] 76/2 indications [1] 32/7 indirectly [1] 68/20 individual [1] 26/23 individuals [2] 45/14 74/20 induce [1] 28/19 induced [1] 69/22 ineffectively [1] 55/16 information [3] 30/25 71/9 74/2 ingest [2] 17/21 23/19 ingested [8] 23/13 23/14 23/22 23/23 25/4 27/23 40/16 60/22 ingesting [5] 27/7 27/11 27/12 39/11 39/12 ingestion [4] 27/4 27/20 28/5 60/6 inhale [1] 26/17 inhaling [2] 26/25 27/10 inherent [1] 65/2 initially [1] 43/22 inject [3] 24/4 24/5 24/6 injected [3] 23/18 24/8 24/18 insignificant [1] 53/9 instance [1] 57/8 instances [2] 60/5 60/13 Instead [1] 41/24 Institute [1] 37/4 institution [1] 5/10</p>
<p>G</p> <p>gang [1] 22/20 gangs [1] 23/5 gastric [1] 25/14 gave [2] 57/7 57/23 general [5] 18/24 31/10 31/19 37/19 62/8 generation [1] 12/9 get [12] 3/19 3/24 7/10 8/15 13/10 18/8 19/17 40/4 43/25 50/8 58/17 66/14 getting [2] 18/9 48/9 Geusau [2] 66/6 73/24 Gill [1] 74/13 give [9] 39/7 53/7 60/10 60/10 62/8 62/11 62/21 64/23 65/3 given [4] 17/14 18/11 50/12 78/13 gives [3] 32/6 34/22 65/4 global [3] 10/7 10/13 10/17 globally [1] 42/13 go [6] 4/6 4/18 17/8 40/3 40/4 46/15 going [10] 3/22 6/24 21/16 40/7 62/8 62/11 63/3 64/7 65/7 67/24 gone [4] 30/19 31/17 31/19 31/20 good [4] 3/2 57/2 57/3 72/4 got [4] 33/6 33/7 43/11 63/21 gotten [1] 56/6 government [17] 4/21 7/4 24/7 24/8 29/21 32/2 38/11 46/4 50/13 51/17 53/6 55/18 56/23 58/22 67/11 69/6 73/17 government's [2] 12/19 69/2 graders [3] 31/7 31/7 31/7 great [3] 66/14 72/15 72/21 Great Britain [1] 72/15 greater [3] 51/3 59/19 65/14 greatly [1] 43/14 ground [1] 3/18 group [6] 40/7 41/17 41/18 41/19 42/16 52/21 groups [2] 54/12 74/17 guess [1] 70/10 guns [1] 22/20</p>	<p>H</p> <p>H-a-l-p-e-r-n [1] 3/15 had [14] 4/19 23/17 30/15 32/20 43/7 44/9 46/16 50/4 54/13 57/25 60/22 65/17 66/13 66/17 hair [1] 40/18 half [1] 33/9 halfway [1] 22/4 hallucinations [1] 5/16</p>	

<p>I</p> <p>insufficient [1] 53/2 integrative [1] 5/9 interest [3] 38/15 62/25 71/4 interested [2] 71/21 78/17 interesting [1] 42/24 international [2] 72/16 72/18 interpret [1] 31/14 interview [2] 40/23 67/14 interviewed [2] 5/25 48/15 intoxicants [1] 44/10 intoxicated [1] 56/6 intoxication [1] 18/17 intravenously [1] 24/18 invalidate [2] 10/10 38/3 invariably [1] 22/18 inverse [1] 63/14 investigation [1] 75/10 invited [1] 6/20 involved [3] 16/23 22/17 32/3 involvement [1] 41/12 involving [6] 6/9 9/10 13/8 13/8 48/7 48/10 IQ [1] 65/6 is [192] issue [1] 75/4 issued [1] 30/4 issues [4] 5/8 6/3 6/10 47/23 it [124] it's [60] 6/6 10/3 12/25 15/8 17/17 18/15 18/15 18/23 18/23 18/25 19/2 19/23 20/25 21/2 22/8 22/10 22/24 23/4 23/9 23/11 25/8 25/12 26/22 27/5 27/5 29/8 30/19 31/19 32/4 33/4 33/19 35/6 35/6 35/20 35/22 37/11 37/22 39/3 49/14 54/19 55/9 55/14 55/15 56/4 58/25 60/16 62/24 63/5 64/3 64/4 67/4 67/6 67/13 68/22 70/6 70/24 72/13 72/23 72/23 76/7 its [4] 19/3 37/3 54/10 61/16 itself [2] 18/25 34/22</p>	<p>66/13 68/14 68/25 72/13 72/20 76/3 76/9 knowledge [3] 16/9 27/20 30/20 known [5] 9/17 29/8 39/7 64/16 64/22</p> <p>L</p> <p>laboratory [3] 5/9 39/6 39/22 land [1] 19/24 language [2] 50/24 53/20 large [2] 61/13 66/2 larger [3] 37/11 44/2 44/23 largest [5] 37/2 37/3 37/12 42/5 60/21 last [6] 15/6 15/14 28/6 40/13 46/16 48/24 late [1] 29/16 latest [1] 51/7 Laverse [1] 74/15 law [1] 56/5 lawyers [1] 37/20 layman's [1] 19/8 lead [2] 3/22 12/9 leading [3] 18/22 19/23 26/5 leads [1] 19/22 least [2] 17/25 44/5 led [1] 50/4 legal [3] 53/10 72/8 72/11 legitimate [1] 47/6 length [1] 63/15 less [7] 8/10 8/12 12/23 14/16 14/24 18/25 39/14 let [4] 37/14 40/24 46/20 63/19 let's [2] 13/13 36/17 letter [2] 47/25 50/25 letters [5] 6/21 47/9 47/13 47/19 48/2 level [2] 33/24 36/20 levels [3] 9/19 9/25 10/14 licensed [1] 4/4 lie [1] 65/13 life [5] 21/17 42/21 53/4 65/5 65/8 life-saving [1] 65/8 lifestyle [3] 22/9 22/13 22/13 lifetime [3] 59/22 60/3 63/13 like [29] 6/18 7/7 17/8 19/5 25/2 27/6 27/8 35/10 38/17 38/23 42/23 43/11 43/12 45/6 46/6 47/8 50/24 51/11 53/24 61/15 63/24 66/17 68/13 69/24 70/5 71/18 72/17 73/18 74/22 likely [3] 24/12 28/9 63/5 likes [1] 63/24 limitations [1] 72/2 limited [1] 17/20 limits [1] 21/15 LINE [2] 79/4 80/4 link [2] 28/15 29/5 liquid [1] 25/14 listed [4] 35/2 35/5 71/4 72/19 literature [17] 8/3 11/6 21/21 29/6 32/12 35/22 37/6 37/8 37/10 39/25 43/12 43/19 49/16 50/2 54/16 66/11 76/10 little [5] 19/18 30/17 31/18 32/23 44/9 lives [2] 19/15 21/18 Livingston [1] 4/19 local [1] 24/9 logic [1] 70/17 long [3] 39/9 54/9 67/8 longer [3] 11/5 20/18 26/18 Longwood [1] 4/12 look [9] 13/7 16/5 19/4 19/10 32/5 35/24 58/13 68/23 74/25 looked [2] 32/14 75/17 looking [11] 6/17 11/25 14/6 19/8 32/19 36/6 54/9 57/11 60/11 60/15 65/22 looks [2] 6/18 46/6 loosely [1] 35/21 loss [2] 10/21 13/12</p>	<p>lot [2] 3/17 76/6 low [1] 73/3 lower [4] 15/19 15/20 15/20 59/3 lung [2] 26/5 26/12 lungs [4] 25/19 25/21 25/23 26/17</p> <p>M</p> <p>M.D [3] 1/18 3/10 77/10 Mageetty [1] 74/14 magnitude [3] 6/5 37/11 60/18 maintenances [1] 61/23 majority [7] 17/19 23/19 24/22 25/15 27/8 39/25 75/7 make [3] 23/6 23/9 38/7 makes [1] 26/21 making [2] 8/25 65/25 male [1] 66/7 man [1] 3/19 many [8] 21/12 21/12 21/12 23/7 33/17 58/17 64/25 72/7 MAPS [5] 71/8 71/13 71/17 71/18 71/21 March [2] 29/23 31/5 marijuana [21] 15/24 15/25 16/2 25/7 25/7 25/17 25/18 25/25 26/9 26/11 26/14 26/25 27/2 27/3 27/6 27/12 32/17 33/7 55/23 56/7 56/10 marked [4] 7/6 50/14 51/19 56/24 market [1] 64/18 marketed [4] 55/2 55/6 55/15 55/16 marketing [1] 55/11 marriage [1] 78/16 mass [1] 10/13 massive [1] 10/8 matter [3] 25/20 77/4 78/17 matters [2] 3/24 57/5 may [14] 26/14 33/25 37/21 38/3 43/17 43/20 43/21 52/16 52/18 53/18 64/24 65/9 67/18 69/5 maybe [3] 13/7 43/5 63/23 McCann [5] 10/20 11/2 61/8 61/19 73/24 McCarthy [5] 16/17 16/20 30/22 30/24 54/23 McLean [1] 5/4 MDMA [145] MDMA's [1] 8/19 MDMAs [1] 15/5 me [11] 7/2 36/4 37/14 40/24 46/20 60/10 63/19 64/7 66/14 69/11 77/12 mean [9] 37/18 46/15 49/12 49/12 52/12 62/22 63/18 67/13 73/4 meaning [1] 53/12 meaningful [2] 52/9 52/14 measure [3] 32/5 34/12 44/16 measures [13] 11/25 12/7 12/18 13/5 19/10 42/2 42/12 42/23 44/16 44/20 52/22 53/19 63/7 median [2] 59/22 60/14 medical [7] 3/25 4/20 5/12 5/14 19/11 64/23 68/17 megalomelia [1] 28/20 member [2] 71/17 72/16 memory [6] 13/12 53/18 53/22 65/19 65/21 66/23 mental [2] 5/7 19/11 mentioned [13] 10/12 11/8 13/4 14/9 18/10 30/6 31/21 37/16 42/4 44/12 57/6 59/5 74/21 merely [1] 52/24 mess [1] 22/11 message [4] 53/3 67/6 67/16 73/9 messages [2] 55/9 69/6 metabolic [1] 62/9 metabolism [1] 62/10 metabolite [1] 62/16 metabolizing [1] 62/5</p>
<p>J</p> <p>Jacobsen [2] 65/16 73/24 Jager [2] 66/21 73/24 JBW [1] 1/8 job [1] 29/21 JOHN [4] 1/18 3/10 3/14 77/10 Johnson [1] 29/23 joints [1] 27/3 journal [5] 45/17 46/7 46/11 46/23 51/5 journals [2] 45/19 45/22 judge [1] 54/23 just [40] 3/22 3/24 7/9 12/25 15/4 18/18 19/2 19/7 22/8 28/12 30/5 32/4 34/10 39/16 40/21 41/21 46/20 47/8 47/9 47/15 49/15 50/15 54/19 54/22 56/12 57/4 57/24 59/2 60/12 63/19 65/21 66/13 66/15 66/16 66/17 69/20 70/12 72/17 73/15 76/7 Justice [2] 30/4 31/2</p>	<p>K</p> <p>kids [2] 40/7 48/13 killers [1] 18/22 killing [3] 36/7 36/9 64/11 kind [5] 3/24 37/3 40/15 41/5 42/5 Kish [11] 10/4 10/25 47/22 60/24 61/5 61/6 63/12 63/18 63/20 63/25 73/23 Kish's [2] 10/10 10/12 KITT [3] 1/21 78/7 78/23 know [44] 8/24 12/20 12/23 15/4 19/4 19/9 19/15 20/25 21/2 21/6 21/9 22/5 23/16 24/9 26/12 31/17 33/5 33/22 35/8 37/22 38/5 39/9 39/10 39/11 40/5 41/4 41/15 43/19 46/14 49/2 50/23 53/20 53/25 55/6 55/12 61/25 62/6</p>	

<p>M</p> <p>methodological [1] 37/9 methodology [2] 10/24 13/22 metrics [1] 13/7 Michael [1] 74/15 Michigan [1] 29/24 might [3] 18/19 55/2 62/19 milked [1] 65/12 million [2] 30/15 33/9 milliseconds [1] 52/17 minutes [1] 18/9 miscitation [1] 50/5 misdescription [1] 50/5 misquoting [1] 55/3 misrepresents [1] 50/19 mistaken [1] 31/9 misuse [1] 56/16 moderate [3] 42/16 43/2 45/5 money [1] 20/16 monkey [1] 62/6 monkeys [3] 62/3 62/18 64/15 MOORE [2] 2/9 56/25 morbid [1] 19/5 more [41] 8/10 8/15 10/5 10/24 10/24 13/10 15/5 17/7 19/2 19/18 21/6 21/10 21/11 24/12 25/25 26/14 26/22 28/22 34/25 37/8 38/16 41/18 42/20 50/8 53/5 54/6 55/8 59/8 60/22 60/22 62/8 62/8 63/9 65/4 66/13 66/14 67/24 69/25 73/13 75/22 76/2 Morgan [2] 14/2 16/3 morning [3] 3/2 57/2 57/3 most [19] 13/19 21/17 26/10 30/7 32/11 35/24 36/5 37/2 39/5 43/12 43/23 43/23 56/5 56/7 57/11 62/23 63/5 68/3 69/5 mouth [1] 63/19 move [1] 7/7 moving [2] 21/17 50/15 MR [2] 3/16 73/14 Mr. [3] 57/5 59/9 70/24 Mr. Scolnick [3] 57/5 59/9 70/24 MS [1] 56/25 much [17] 5/22 10/23 12/2 14/16 18/25 21/10 21/16 23/3 26/22 26/22 34/6 41/24 44/2 53/17 59/3 59/3 61/17 multiple [3] 39/23 56/2 66/24 music [2] 55/7 55/8 must [2] 70/2 70/21 my [21] 4/21 4/22 4/22 5/9 5/15 5/23 8/11 10/19 15/3 41/4 48/5 58/25 59/2 59/19 60/11 63/10 65/21 66/16 66/19 74/15 78/19 myself [3] 8/25 24/6 70/16</p>	<p>neurocognitive [2] 69/9 70/3 neurocognitive [2] 54/9 61/22 neuron [6] 36/7 36/13 36/15 53/24 53/25 54/2 neurons [4] 61/2 69/12 69/13 70/14 neurophysiological [1] 69/16 neurotoxic [5] 9/12 63/22 64/10 64/14 70/19 neurotoxicity [8] 35/16 35/19 36/6 36/12 36/13 64/8 70/11 70/22 never [5] 37/19 67/19 67/19 70/5 70/5 new [21] 1/3 1/19 1/20 1/23 2/8 2/11 2/14 11/15 16/18 48/6 48/7 48/7 48/7 48/8 48/8 48/16 49/11 49/12 78/4 78/6 78/8 newer [1] 10/5 next [4] 21/9 39/16 48/20 76/11 nice [1] 72/13 nicotine [3] 15/17 18/21 26/19 NIDA [1] 68/6 night [1] 40/3 no [28] 1/8 8/13 10/7 10/9 10/13 11/5 14/17 17/17 21/11 22/24 27/5 27/21 29/2 30/24 36/16 38/2 42/11 44/9 45/10 49/14 55/14 63/24 67/4 67/16 73/10 74/8 75/18 78/16 Nobody [1] 73/9 non [4] 9/20 34/20 42/14 57/12 non-data [1] 57/12 non-database [1] 34/20 non-users [2] 9/20 42/14 none [3] 12/12 46/17 74/19 nonhuman [1] 62/10 normally [1] 50/23 normative [1] 52/23 nose [1] 27/10 not [77] 10/6 11/22 11/23 11/24 12/10 12/15 16/16 17/17 17/21 18/11 21/4 21/7 22/24 23/4 23/11 24/13 24/18 25/11 25/20 26/11 27/5 27/5 27/21 28/4 28/9 29/3 29/19 31/8 34/16 35/2 35/5 36/8 36/16 38/9 39/10 39/24 40/9 41/20 43/2 43/6 44/24 45/10 45/11 46/21 47/10 47/10 47/15 48/2 49/14 52/8 54/2 55/11 55/14 55/19 57/24 58/6 58/9 58/25 59/20 60/6 60/17 61/25 62/19 63/20 63/25 65/7 66/18 68/3 68/11 68/24 71/16 71/18 71/22 72/10 75/15 76/5 78/14 Notary [3] 1/22 77/15 78/7 noted [4] 21/21 72/7 73/3 77/5 nothing [2] 14/17 77/3 Notice [1] 1/21 noticed [1] 21/20 now [21] 7/7 8/4 12/2 14/9 19/17 28/13 29/5 29/11 29/15 35/10 35/11 38/23 44/11 45/24 50/9 52/5 54/4 54/14 64/19 70/15 75/16 nowhere [2] 54/17 64/2 number [28] 6/13 13/17 13/18 14/10 15/11 20/2 22/6 27/14 33/3 33/10 42/24 51/23 57/23 58/3 58/6 58/16 58/17 58/19 60/5 60/6 60/8 60/13 60/14 73/18 73/21 74/10 74/12 74/20 numbers [4] 34/25 57/7 58/5 59/2 Nut [2] 13/20 71/24 Nut's [2] 16/5 16/5</p>	<p>offered [4] 14/17 30/25 49/6 60/13 offering [1] 50/9 OFFICE [1] 2/5 official [1] 61/8 often [1] 49/5 Oh [1] 71/23 Okay [29] 3/6 3/22 6/24 8/8 17/8 23/12 23/21 28/13 29/13 29/14 31/21 34/9 35/14 37/14 38/15 40/24 47/2 47/20 50/7 56/22 57/22 60/20 60/24 61/19 62/3 62/12 63/11 66/5 73/2 olds [1] 31/8 ominous [1] 45/10 omits [1] 50/19 once [1] 67/20 one [32] 2/13 14/2 14/19 17/25 18/6 18/22 19/23 21/6 21/24 26/8 32/4 33/10 35/21 35/24 36/5 36/25 41/14 41/17 42/4 45/19 45/21 45/25 47/3 48/12 52/21 54/12 54/22 55/5 58/9 66/17 69/5 75/12 ones [2] 41/5 43/22 ongoing [1] 7/25 only [6] 11/23 41/5 42/6 43/2 53/5 74/5 opinion [8] 8/6 8/12 16/25 48/5 49/5 59/19 63/10 75/6 opinions [1] 14/6 opportunity [1] 53/7 oppose [1] 76/4 opposed [1] 35/7 opposition [1] 50/3 oral [1] 62/13 orally [4] 23/14 23/20 25/4 25/10 order [2] 6/5 58/12 order [32] 8/8 12/18 13/9 13/23 16/12 16/24 18/18 25/9 36/4 37/7 39/11 40/11 40/18 40/21 40/25 41/7 41/18 41/19 42/22 43/12 44/9 52/21 53/10 53/19 53/23 54/22 56/8 59/25 61/3 61/11 74/17 75/13 other's [1] 50/5 others [2] 56/16 67/25 otherwise [2] 8/14 14/18 our [20] 9/3 13/2 22/10 25/21 32/9 37/25 43/4 44/18 46/18 47/11 47/12 47/21 48/2 60/16 60/21 65/14 68/3 72/9 72/22 74/13 out [6] 26/4 29/24 43/12 55/17 69/20 69/25 outcome [1] 78/17 outcomes [1] 61/2 over [15] 8/22 20/17 32/23 39/8 50/2 52/21 53/6 53/11 56/23 60/3 60/15 61/12 62/25 63/8 75/13 over-the-counter [1] 53/11 overall [2] 31/19 58/18 overdose [1] 19/22 overdrive [1] 28/20 overlap [2] 72/22 74/18 overview [1] 51/15 own [3] 16/21 19/3 66/19 oxygen [1] 68/16</p>
<p>N</p> <p>NADIA [1] 2/9 name [1] 48/24 narcissistic [1] 28/20 narrow [1] 41/22 nasally [1] 23/16 national [5] 6/8 29/25 30/14 37/4 58/13 native [2] 54/11 54/13 nature [1] 59/16 near [4] 15/25 35/7 38/10 54/18 necessarily [1] 72/10 need [3] 16/5 53/6 65/20 needles [2] 24/12 24/20 needs [1] 75/17 negative [1] 20/8 neither [1] 44/3 Nestler [1] 70/8 Netherlands [1] 48/13 Network [1] 32/2 neuro [3] 40/15 69/9 70/3</p>	<p>O</p> <p>oath [1] 3/8 observed [1] 19/12 obtain [3] 31/23 44/3 67/23 obvious [3] 12/15 15/8 38/7 obviously [5] 8/12 12/18 18/15 39/15 66/13 occasion [1] 21/7 occur [2] 28/4 69/16 occurred [1] 73/19 occurring [1] 9/16 occurs [2] 17/22 28/5 off [2] 20/12 65/5 offer [2] 6/25 51/11</p>	<p>P</p> <p>p.m [1] 77/5 pack [1] 26/9 page [3] 76/11 79/4 80/4 PAGE/LINE [2] 79/4 80/4 paper [13] 13/24 16/4 26/25 49/18 49/23 60/12 61/10 61/24 65/21 70/15 70/23 71/5 72/6 papers [3] 15/7 72/3 74/8 Parkinson's [1] 12/12 Parrot [9] 17/24 18/5 47/22 48/24 50/11 51/14 60/16 63/23 71/2 Parrot's [6] 18/8 49/23 50/17 50/18 51/5 51/9 part [4] 23/6 28/6 34/20 68/8 participants [1] 48/7</p>

<p>P</p> <p>participated [1] 45/15 particular [1] 58/9 Particularly [1] 10/3 parties [3] 40/4 40/8 78/15 party [1] 42/10 past [3] 25/24 64/20 65/24 pathological [2] 17/22 20/17 pathologically [1] 54/20 pathology [1] 41/23 patients [3] 22/2 22/15 23/17 pattern [5] 21/5 23/3 28/5 28/9 68/21 patterns [3] 22/22 29/20 36/3 peaked [2] 31/15 31/16 peer [7] 6/19 43/15 45/16 45/18 46/22 49/22 51/2 people [53] 5/20 6/2 6/7 12/4 12/21 15/11 16/23 17/19 19/24 20/2 20/14 21/4 21/12 21/16 21/17 22/6 22/16 23/7 23/15 23/19 24/4 24/5 24/25 25/3 25/10 25/11 25/16 26/8 26/15 27/9 27/17 30/15 33/7 33/9 33/14 33/15 38/9 40/3 42/10 43/12 43/15 43/20 43/21 44/15 48/16 55/11 55/25 67/19 67/21 67/23 68/19 69/22 75/2 people's [5] 19/6 19/15 19/19 20/9 75/20 percent [8] 24/25 31/11 33/20 34/7 58/5 58/6 58/7 58/8 percentage [3] 34/12 57/24 58/10 perfect [1] 37/23 perfectly [1] 37/20 perform [1] 52/17 performance [16] 19/13 42/12 42/22 45/14 52/23 53/2 53/3 53/9 53/13 63/6 65/9 66/7 66/23 68/16 75/3 75/15 perhaps [4] 13/10 30/12 41/8 42/5 period [3] 20/18 26/18 40/12 permanent [3] 9/24 12/22 62/2 person [8] 28/21 33/25 40/16 48/5 52/16 54/20 68/22 71/17 perspective [2] 19/8 65/12 Peter [1] 4/19 phase [2] 21/16 63/5 phenformin [1] 64/17 physical [2] 9/13 25/22 physician [8] 8/13 15/3 15/6 64/2 68/18 68/25 75/13 76/5 physicians [3] 14/5 16/13 16/13 physiologically [2] 20/24 62/4 pick [3] 37/21 47/8 47/11 picture [2] 7/9 12/3 piece [3] 61/20 71/4 71/24 pieces [1] 49/6 Pierrepoint [1] 2/13 pill [4] 24/22 25/4 34/4 60/9 pills [7] 21/6 34/4 60/7 60/14 60/15 60/18 60/23 placing [1] 3/8 PLAINTIFF [2] 1/6 2/6 Plaza [3] 1/20 2/7 2/13 please [1] 20/11 plus [1] 30/3 point [7] 11/7 31/14 46/15 46/16 75/14 75/22 76/8 pointed [1] 38/16 points [5] 50/3 65/5 67/9 69/20 69/25 poly [2] 41/17 41/19 pop [1] 55/10 popular [2] 55/8 55/13 portion [1] 24/19 position [4] 46/6 47/3 69/2 69/3 possible [1] 41/13 post [1] 42/15</p>	<p>potential [2] 12/14 35/12 powder [2] 23/24 59/11 powdered [3] 59/6 59/10 59/17 powerful [2] 28/18 28/22 preclinical [1] 62/7 prefer [1] 67/20 prescription [2] 53/11 71/13 presence [3] 33/23 34/5 40/20 present [9] 12/14 13/2 26/20 27/4 27/19 27/22 33/21 55/5 67/10 presented [2] 30/21 30/24 pressing [1] 63/9 pressure [1] 68/13 pretty [2] 5/22 8/2 prevent [1] 65/7 previously [2] 7/3 34/5 primarily [1] 8/25 primary [1] 21/14 primates [2] 62/6 62/10 prior [9] 34/2 38/9 40/17 41/10 41/11 44/18 44/18 48/13 55/23 priority [2] 71/14 71/16 Prisons [1] 22/4 probably [4] 6/18 36/5 64/7 69/11 probation [1] 22/5 problematic [1] 37/7 problems [8] 37/24 39/15 39/19 39/24 39/25 43/13 43/23 64/25 procedure [1] 44/21 produced [1] 62/15 production [2] 10/8 10/13 professor [2] 5/11 5/12 professorship [1] 5/13 proffer [1] 76/8 profile [1] 19/4 profit [1] 23/11 program [2] 4/7 4/13 prominent [1] 15/12 prominently [1] 13/19 promote [2] 19/5 26/11 promoted [1] 67/17 promotes [1] 28/22 pronounce [1] 64/7 pronouncing [1] 69/11 properties [2] 17/18 26/13 protective [2] 69/9 70/3 protects [1] 69/10 provide [1] 5/6 provided [3] 7/3 40/22 51/17 provision [1] 50/21 psychiatric [1] 40/22 psychiatrist [1] 4/24 psychiatry [3] 4/10 4/12 5/9 psychoactive [1] 28/19 Psychobiology [1] 51/15 psychologic [1] 6/14 psychological [2] 18/16 29/2 psychologically [1] 20/24 Psychology [1] 49/21 psychotropic [1] 72/16 public [12] 1/22 11/25 12/3 12/6 13/5 65/13 65/15 66/2 67/3 69/5 77/15 78/7 publications [3] 6/19 13/19 46/22 publish [2] 43/10 58/22 published [40] 6/13 7/25 10/4 10/20 13/21 13/25 14/2 14/5 16/10 16/14 43/7 45/16 45/18 45/20 45/21 45/25 46/7 46/13 47/16 47/18 48/17 48/18 48/21 49/3 49/7 49/16 50/6 50/16 51/4 51/6 57/12 60/12 60/25 61/20 63/12 66/16 66/19 74/14 74/16 74/22 pure [2] 39/7 44/8 Pursuant [1] 1/21 put [5] 6/4 46/4 47/4 63/19 67/14</p>	<p>Q</p> <p>qualifications [1] 3/20 Quantifying [1] 56/15 question [7] 34/17 38/13 41/24 48/3 53/7 63/9 74/25 questioning [1] 39/20 questions [6] 3/23 38/16 53/5 55/17 73/13 73/15 quite [10] 12/18 25/11 33/4 46/14 55/9 55/25 58/19 67/12 68/4 74/22 quote [9] 17/25 18/2 20/19 34/3 50/18 51/14 54/25 64/14 70/18 quote/unquote [4] 20/19 34/3 64/14 70/18 quoted [1] 31/9</p> <p>R</p> <p>raised [1] 47/24 raises [1] 75/9 raising [2] 50/4 63/20 range [2] 52/23 61/13 rank [2] 13/23 15/17 ranked [5] 14/15 15/19 15/25 16/2 57/21 rare [3] 15/13 35/6 49/21 rate [2] 8/23 34/13 rates [1] 34/14 rather [1] 65/24 ratio [1] 34/21 read [1] 49/9 reading [1] 50/22 real [5] 22/10 32/7 39/17 67/2 68/23 realize [2] 3/18 63/5 realized [5] 11/22 11/24 12/4 12/13 54/18 really [5] 20/13 37/2 43/3 52/20 70/6 rebound [1] 61/12 rebuttals [1] 46/23 recall [3] 15/14 15/18 15/22 received [2] 4/21 49/22 recent [4] 14/4 30/7 32/12 57/11 recently [3] 26/11 40/17 50/6 Reconsideration [2] 51/13 70/25 record [2] 3/4 78/12 red [1] 63/20 reduced [3] 30/16 61/21 66/22 reduces [2] 43/3 69/9 reduction [3] 10/18 31/11 63/16 reference [1] 74/24 referring [1] 12/7 reflected [1] 14/25 reflective [1] 12/18 reformation [2] 64/12 70/13 refresh [1] 65/21 regard [1] 62/5 regarding [21] 7/23 8/16 8/19 9/24 10/15 13/11 14/11 14/13 15/23 17/2 17/3 23/21 31/3 31/23 32/12 35/12 36/19 44/5 45/5 49/4 53/8 reinforcing [2] 12/16 17/18 related [16] 6/2 18/13 26/14 32/17 32/18 33/15 34/10 34/15 34/19 41/10 57/15 62/4 62/15 68/20 68/21 78/15 relating [1] 51/25 relationship [3] 21/22 28/16 63/14 relationships [1] 20/9 relative [8] 8/8 13/9 13/13 13/16 13/21 14/11 34/23 67/18 relatively [2] 44/8 44/24 release [3] 22/3 69/19 70/2 releases [1] 25/13 relevance [1] 72/24 reliable [1] 52/5 relied [1] 11/4 remained [1] 67/8 remains [1] 75/12</p>
---	---	--

<p>R</p> <p>remarkable [2] 22/9 49/20 remarkably [1] 54/19 remember [1] 59/2 removed [2] 42/6 67/2 removing [1] 37/4 repeat [1] 70/16 repeated [1] 69/17 repetitive [1] 17/21 rephrase [1] 34/17 replaced [1] 10/23 replicated [1] 44/23 replied [2] 46/10 47/5 reply [1] 46/13 report [4] 11/11 11/18 11/22 74/19 reported [3] 57/14 57/17 57/19 research [40] 4/15 4/21 4/22 5/15 6/9 7/23 7/25 8/16 8/18 8/21 9/18 11/15 11/17 11/24 13/11 17/15 18/9 18/12 21/21 24/7 26/3 32/10 32/24 35/11 36/19 36/24 45/23 46/22 47/10 48/25 50/19 51/9 51/16 52/5 52/5 52/8 62/7 71/9 74/6 75/14 researcher [3] 5/19 48/24 71/19 researchers [5] 40/25 61/11 72/2 73/2 75/7 reserved [3] 50/24 68/7 68/10 residency [4] 4/7 4/13 4/15 6/6 respect [5] 25/6 25/15 27/7 45/24 75/4 respond [1] 12/10 response [10] 46/5 47/2 47/12 47/16 47/21 48/3 50/11 51/14 60/16 70/25 responses [3] 46/23 47/23 48/9 rested [2] 40/8 40/10 result [2] 9/5 70/9 results [8] 42/8 45/11 52/22 56/17 61/2 69/18 72/10 74/19 resume [2] 6/17 6/25 retackle [1] 46/18 return [1] 9/19 reverse [1] 28/3 reversible [1] 28/2 review [12] 6/19 45/17 45/18 46/23 47/7 49/7 49/9 49/11 49/15 49/22 50/18 51/5 review's [1] 49/25 reviewed [3] 32/11 46/8 51/2 reviews [1] 49/6 right [19] 6/15 13/4 38/20 47/18 47/24 52/4 59/23 64/19 66/20 70/11 71/10 72/3 72/12 73/8 73/12 73/20 73/25 74/3 75/15 risk [11] 13/21 19/4 24/15 27/3 28/24 34/23 35/2 59/19 66/2 67/18 68/19 risks [6] 25/17 26/24 27/11 27/14 27/19 27/21 RMR [2] 1/22 78/23 Rogers [2] 47/22 50/11 roll [1] 27/2 room [17] 12/20 31/22 31/23 32/4 32/12 32/16 32/18 32/21 33/6 33/11 57/6 57/9 57/20 58/9 58/11 58/16 58/18 rooms [2] 13/6 19/24 roughly [3] 6/21 30/16 48/21 routine [1] 70/5 routinely [1] 25/4 RR [1] 56/15 running [1] 71/17</p>	<p>sales [1] 23/6 same [13] 15/6 22/24 23/5 28/25 41/20 48/21 51/5 55/23 61/10 61/17 64/15 68/22 72/18 saving [1] 65/8 say [17] 5/24 14/23 15/17 20/9 22/12 24/21 26/8 33/12 36/5 38/25 40/7 46/24 47/14 54/5 55/14 64/2 70/13 saying [3] 18/5 36/15 68/11 says [1] 20/23 scale [1] 62/20 scene [1] 42/11 Schedule [2] 72/20 72/21 School [3] 4/20 5/12 5/14 science [3] 33/22 37/22 38/7 scientific [9] 9/22 10/16 11/5 13/11 17/11 20/7 35/21 49/19 76/10 SCOLNICK [7] 2/15 3/4 3/16 57/5 59/9 70/24 73/14 score [1] 73/3 Scotland [2] 56/14 56/18 screened [1] 43/22 second [4] 45/21 45/24 60/10 68/8 secondary [4] 35/13 45/9 52/7 75/5 seconds [1] 52/17 see [6] 19/16 60/15 65/20 69/21 70/3 72/13 seeing [1] 12/2 seem [1] 23/8 seen [2] 28/10 70/5 seizures [1] 68/12 self [3] 21/15 34/13 56/16 sense [4] 18/24 34/22 38/2 46/17 Sentencing [6] 7/19 11/4 11/9 11/12 29/12 69/3 separate [3] 55/13 59/20 60/13 serotonin [10] 9/7 9/25 10/8 10/14 10/21 43/9 61/2 61/8 62/16 64/13 serotonergic [1] 64/8 sert [8] 9/18 9/24 10/25 61/12 61/13 61/21 61/25 63/15 serts [2] 9/10 10/6 serve [1] 61/16 services [1] 5/6 set [5] 14/6 34/4 44/2 78/11 78/19 several [2] 21/15 42/20 severe [1] 70/4 shaves [1] 65/5 SHEET [2] 79/2 80/2 shelter [1] 22/4 short [1] 68/6 short-term [1] 68/6 should [7] 28/4 48/3 48/4 72/4 73/9 74/23 74/25 show [6] 24/8 26/4 44/24 46/19 61/12 66/25 showed [9] 26/11 30/6 31/9 33/15 42/25 44/15 44/20 65/17 66/6 showing [9] 12/21 17/17 33/7 33/8 33/9 35/25 54/16 55/18 75/25 shown [1] 70/8 shows [2] 33/19 52/9 significance [5] 43/2 51/3 52/16 63/8 75/16 significant [25] 19/7 33/3 33/4 35/9 36/18 36/20 37/24 41/14 43/17 45/7 45/8 45/13 52/6 52/12 52/19 52/25 54/6 54/16 59/19 60/17 62/15 66/18 72/22 72/24 75/5 significantly [5] 11/18 12/5 14/24 54/6 66/6 similar [3] 53/12 60/18 74/16 since [20] 4/23 6/5 8/20 9/5 9/17 16/10 16/10 16/14 30/7 31/12 48/9 48/17 48/18 49/4 51/4 55/7 56/7 67/22 69/21 71/16 single [6] 21/6 27/24 62/13 67/15 68/24 76/5 situation [1] 68/24 sleep [2] 40/2 40/5 sleeping [1] 39/10</p>	<p>slightly [1] 16/2 slower [1] 52/18 small [3] 58/19 65/25 66/17 smaller [1] 26/22 smoke [1] 26/25 smoked [3] 25/7 25/9 27/6 smoking [7] 23/25 25/11 25/16 25/18 25/24 26/18 56/10 snort [2] 23/16 25/3 snorting [2] 23/24 27/9 so [81] sober [1] 54/14 social [1] 13/7 societal [3] 13/14 13/16 18/13 societies [1] 72/22 society [2] 32/9 68/3 some [37] 8/15 9/15 13/4 13/5 17/8 24/4 24/5 25/11 27/17 32/6 32/7 32/10 33/22 36/2 38/8 38/16 42/21 42/22 42/25 44/15 44/19 45/4 46/21 48/17 51/24 55/8 61/11 61/17 64/24 64/25 67/19 67/24 74/16 74/18 74/18 75/8 75/14 somebody [7] 15/15 21/8 26/18 26/20 41/21 52/18 63/23 somehow [1] 27/23 something [6] 18/5 38/24 49/20 52/15 70/2 71/21 sometimes [1] 43/16 somewhere [1] 30/14 sorry [4] 27/12 56/20 59/13 60/21 sort [2] 9/15 37/11 sorting [1] 44/21 sorts [1] 53/21 sounds [6] 6/23 27/8 38/17 38/23 45/6 73/18 sourced [1] 24/8 Southern [1] 16/18 speak [2] 15/2 71/15 speaking [2] 8/20 16/24 specialist [1] 71/10 specific [5] 5/15 30/23 32/6 50/24 55/11 specifically [1] 8/9 specifics [1] 7/11 speedball [1] 24/5 spend [1] 20/15 split [1] 42/15 spoke [1] 70/24 squirrel [2] 62/3 62/18 SSC [1] 11/11 stages [1] 22/3 standard [2] 47/14 74/24 standpoint [2] 12/3 68/17 stands [1] 35/11 start [2] 3/7 13/13 started [2] 3/19 55/16 state [9] 1/22 7/23 8/16 17/15 25/2 25/14 52/4 78/4 78/8 statement [3] 18/7 72/14 76/4 STATES [12] 1/2 1/5 1/18 12/22 16/17 25/8 29/10 37/13 72/17 72/19 72/20 72/25 statistical [5] 41/25 42/25 52/15 52/19 52/25 statistically [2] 35/7 43/17 statistics [2] 6/9 15/22 stats [1] 48/8 status [1] 72/9 stay [2] 9/14 69/7 staying [1] 39/6 still [12] 8/6 29/17 55/5 60/11 64/20 67/6 67/12 67/23 68/22 74/23 75/13 75/17 stimulant [1] 28/19 stop [4] 21/18 37/14 40/24 46/20 stops [2] 21/13 28/3 strategy [1] 44/20 strike [1] 41/8</p>
<p>S</p> <p>sad [1] 70/6 sadly [1] 67/12 safe [5] 34/3 67/16 67/20 73/10 73/11 safer [5] 13/3 15/7 33/13 69/4 76/7 safety [1] 67/18 said [7] 15/7 19/18 28/12 28/25 52/13 53/24 67/20</p>		

<p>S</p> <p>stroke [2] 19/22 69/22 stronger [1] 38/8 strongly [1] 27/15 studies [39] 9/4 13/15 13/23 14/10 14/13 14/20 14/22 15/16 15/20 15/24 16/8 16/9 16/12 29/23 37/2 38/18 41/3 41/4 41/7 41/17 42/5 43/24 44/5 45/2 45/3 48/6 49/12 49/15 50/2 51/24 60/2 65/22 66/17 72/4 73/18 73/19 74/5 74/10 74/12 study [30] 10/4 10/10 14/5 16/6 29/12 29/15 37/3 37/9 37/12 37/20 37/23 38/8 38/21 39/6 41/12 42/6 43/7 43/14 44/23 48/10 48/12 52/19 54/9 56/13 59/21 59/22 60/25 61/6 63/12 64/5 stunned [1] 50/22 subject [2] 39/6 72/17 subjects [2] 13/12 44/6 Subscribed [1] 77/12 subsequent [3] 16/20 70/7 74/14 substance [10] 5/6 6/9 6/14 7/8 9/17 29/25 45/22 56/8 56/16 63/3 substances [7] 6/14 13/9 13/17 14/12 31/24 36/4 39/11 substantial [1] 24/19 substantially [1] 69/4 substantive [2] 3/24 10/10 successive [1] 21/7 such [15] 10/17 12/19 13/24 19/11 20/13 21/5 34/18 63/7 66/4 67/8 68/12 72/14 72/23 76/8 78/12 suffering [2] 5/7 6/2 suggest [1] 35/4 suggested [1] 60/2 suggesting [1] 14/18 suicide [3] 34/14 34/14 34/19 summarize [1] 52/3 summary [1] 28/11 supplemental [1] 65/10 support [1] 45/12 supportive [1] 75/19 suppression [1] 24/10 sure [8] 3/21 6/6 23/5 24/24 62/19 65/21 66/3 68/11 surmount [1] 21/11 surveillance [1] 75/11 surveilling [1] 29/22 survey [5] 30/2 30/8 30/14 56/17 58/14 surveyed [2] 14/5 15/2 surveying [1] 31/6 survive [1] 63/2 swallow [1] 25/10 sworn [3] 3/11 77/12 78/11 symptoms [2] 68/7 68/10 system [1] 8/21 systems [2] 22/21 22/25</p>	<p>tars [1] 26/2 task [2] 49/24 66/7 taurine [2] 69/8 69/19 techniques [1] 11/16 technology [2] 9/5 10/6 teenagers [2] 31/4 55/21 teens [2] 29/16 55/2 TELEPHONIC [1] 1/17 tell [1] 36/23 temperature [1] 25/13 temporary [1] 28/8 ten [1] 43/19 tend [1] 26/16 tends [1] 26/3 tenth [1] 31/7 tenth graders [1] 31/7 term [3] 35/15 54/9 68/6 terms [2] 18/23 35/21 test [4] 42/23 44/14 44/16 66/9 tested [1] 40/4 testified [4] 3/13 7/15 8/4 17/24 testimony [3] 7/8 19/20 78/13 testing [5] 40/14 40/15 42/15 62/13 63/4 tests [3] 39/18 44/13 65/19 thalamus [1] 62/17 than [32] 8/10 8/13 12/23 13/3 14/16 14/24 15/8 15/19 15/20 15/20 16/2 17/7 19/2 24/16 25/25 26/18 28/22 33/13 39/14 41/18 42/20 52/18 54/7 56/8 59/3 59/19 60/23 65/15 67/25 75/23 76/2 76/7 thank [7] 14/8 21/19 35/10 54/22 56/11 73/12 77/2 that [412] that's [40] 5/15 6/16 10/22 10/22 11/19 11/23 16/7 16/19 16/19 22/14 27/17 33/21 34/16 34/20 37/12 39/2 43/11 46/25 47/13 47/15 49/17 55/11 58/12 59/18 60/4 60/5 60/6 60/20 61/9 63/3 63/9 65/24 66/10 70/11 73/6 73/7 73/10 73/25 74/4 75/16 their [24] 14/6 14/13 15/12 19/11 21/18 22/7 23/6 23/8 26/17 34/3 40/22 41/2 42/21 44/6 47/24 62/23 69/23 71/5 71/15 71/15 72/2 72/8 73/3 75/3 them [20] 15/4 16/6 16/23 18/6 22/5 23/9 33/17 39/7 39/21 42/25 44/22 48/15 53/7 53/21 53/22 59/20 65/23 67/23 73/21 74/19 themselves [2] 21/3 23/4 then [21] 4/21 9/17 12/8 13/10 20/18 20/19 21/15 39/7 39/8 43/5 43/11 47/11 48/15 48/22 56/12 57/22 58/15 61/10 67/18 70/19 71/24 theorized [1] 32/9 there [69] 9/23 10/13 10/17 10/21 12/8 12/11 12/13 14/4 14/12 16/12 16/25 22/24 23/5 23/15 24/15 24/19 25/17 25/19 25/22 25/23 25/24 26/19 26/19 27/10 27/22 29/5 30/25 31/10 31/22 33/9 33/16 34/6 34/11 34/11 34/18 37/14 37/19 38/6 39/19 40/24 41/7 41/9 43/13 45/7 45/12 46/20 47/2 48/6 48/12 48/16 51/23 52/5 53/10 54/15 58/3 58/8 61/8 63/14 64/24 66/3 66/24 72/21 73/3 74/10 74/12 74/17 75/8 75/18 75/21 there's [32] 7/24 8/21 9/4 9/15 9/15 10/7 10/9 10/19 13/18 13/23 14/16 14/17 19/12 20/18 21/10 22/18 23/3 23/7 27/14 29/20 35/25 38/2 38/4 39/15 39/23 61/13 61/15 64/25 67/4 68/24 73/10 74/8 these [22] 11/15 16/8 16/9 22/20 28/14 34/10 34/13 34/15 35/21 38/8 38/18 39/17 41/2 41/16 41/25 42/7 43/16 53/8 65/11 65/22 70/4 74/5 they [33] 14/15 20/15 20/16 20/19 20/19 20/21 20/22 20/23 20/25 21/2 21/5 24/6 25/2 25/2 26/17 28/21 28/22 31/9 33/18 34/2 34/5</p>	<p>39/12 40/4 40/8 40/8 40/22 47/24 55/22 64/16 64/20 66/25 69/24 74/7 they're [8] 22/4 39/9 39/10 40/5 40/9 40/10 43/25 59/18 they've [2] 30/2 56/9 thing [5] 12/25 39/17 41/20 64/4 64/10 things [6] 12/13 19/5 38/4 38/6 38/8 68/13 think [11] 8/2 10/23 13/4 13/6 30/16 31/9 33/25 52/12 55/4 58/24 74/14 thinking [1] 22/15 thinks [2] 67/15 67/16 this [61] 3/3 7/15 9/22 11/6 13/19 15/13 16/16 17/21 20/12 20/17 20/20 21/13 21/16 22/9 23/7 25/16 27/9 28/4 30/20 31/14 31/15 32/14 37/21 38/12 38/23 42/5 44/24 45/15 45/16 49/11 50/12 50/16 50/21 50/25 51/7 51/7 51/17 51/21 54/10 57/11 57/12 63/20 64/5 64/7 67/7 67/14 67/16 69/4 69/12 70/21 71/4 72/6 74/2 74/25 75/22 76/6 76/8 77/13 78/15 78/17 78/19 those [44] 5/7 11/20 12/4 12/4 12/13 13/12 14/13 15/7 15/16 15/19 15/24 19/3 22/22 25/2 25/3 26/15 27/19 27/21 29/3 33/5 37/23 39/9 39/23 39/25 41/6 42/17 42/18 42/19 45/14 46/17 47/13 47/19 47/25 48/15 53/15 53/21 54/11 57/17 64/15 64/18 65/12 68/2 73/18 75/11 though [4] 20/25 21/2 35/3 65/8 thousand [1] 6/7 thousands [3] 5/25 16/22 74/8 three [1] 40/17 through [9] 3/23 21/20 21/21 23/24 23/24 26/4 27/10 46/15 68/21 throughout [1] 10/22 61/9 tightening [2] 27/15 tightly [1] 37/8 time [22] 5/22 8/22 9/18 15/14 16/16 17/20 26/18 28/3 33/20 38/15 39/8 48/2 48/21 55/5 55/23 59/15 61/12 62/25 63/8 67/8 70/4 77/5 timed [1] 44/22 times [5] 6/13 15/11 42/18 42/20 42/20 timing [1] 16/8 tips [1] 58/25 Tishkent [1] 26/5 tissue [2] 24/9 27/16 titled [1] 70/25 tobacco [8] 15/21 18/20 25/25 26/10 26/15 26/20 26/21 27/6 today [9] 3/5 3/18 7/3 7/8 8/6 8/17 29/18 30/12 51/18 tolerance [1] 21/8 tons [1] 65/23 too [1] 70/21 took [1] 51/3 top [3] 45/22 71/14 71/16 total [8] 57/8 57/9 57/14 57/17 57/19 57/24 58/8 58/14 towards [1] 6/6 toxic [5] 9/16 61/2 62/21 65/3 69/21 toxicity [1] 35/25 track [1] 8/21 training [3] 4/13 4/22 4/23 transfer [1] 9/13 transitioning [1] 22/5 transmission [1] 24/11 transporter [3] 9/7 10/9 61/9 transporters [2] 10/7 10/21 trauma [1] 44/18 treated [3] 5/25 16/23 19/25 treatment [1] 14/13 treaty [1] 72/16 tremendous [4] 7/24 20/15 22/19 75/25 trends [2] 29/20 42/25</p>
<p>T</p> <p>tablets [1] 60/3 tachycardia [1] 68/12 take [12] 7/9 21/6 23/16 25/4 48/2 52/15 52/18 53/2 60/2 65/6 67/6 73/9 taken [1] 34/2 takes [2] 21/8 28/3 taking [3] 21/11 25/20 49/24 talk [4] 28/13 36/17 49/8 67/17 talked [6] 14/20 16/21 34/9 50/15 59/15 73/23 talking [7] 3/19 7/10 31/3 41/10 51/8 58/7 59/16 tapping [2] 42/23 44/12 tar [1] 26/9 target [1] 68/2</p>		

T	V	
<p>tried [2] 30/15 40/25 trouble [1] 20/3 true [4] 3/25 25/6 73/7 78/12 truly [1] 39/12 truth [1] 43/21 try [2] 8/24 46/18 trying [4] 31/14 38/18 43/25 47/11 turn [5] 29/11 35/10 53/6 56/23 61/11 turning [3] 59/21 70/23 71/24 turnover [1] 43/10 twelfth [1] 31/7 twice [1] 45/2 two [9] 13/8 26/10 41/4 44/5 45/2 45/3 45/21 52/20 71/7 type [2] 12/6 66/11 types [2] 13/12 37/5 typical [2] 22/23 55/9 typically [9] 21/5 22/14 23/14 23/22 23/23 24/18 25/7 25/9 28/14</p>	<p>valid [1] 55/5 validate [1] 63/25 value [2] 37/25 66/18 valves [1] 27/25 variable [2] 29/9 74/21 variant [1] 24/2 varies [1] 72/9 various [2] 28/15 31/24 vast [6] 17/19 23/19 24/21 25/15 39/24 75/7 vegetative [1] 25/20 verbal [2] 53/18 53/22 versed [1] 8/2 versus [3] 16/17 59/7 76/4 very [20] 18/23 21/9 22/9 22/12 29/9 33/12 35/22 39/4 49/21 49/22 50/23 51/4 61/10 61/13 64/3 64/4 64/15 64/18 65/25 72/11 Vicodin [1] 53/20 victims [1] 69/21 violence [2] 22/19 29/7 violent [2] 28/17 29/10 virtually [1] 37/22 visited [1] 57/25 visits [21] 12/20 31/22 31/23 32/4 32/13 32/21 33/11 34/9 57/7 57/8 57/10 57/14 57/16 57/18 57/19 57/23 57/24 58/4 58/5 58/9 58/16 volatilizing [1] 25/12 volunteer [1] 43/23 Von [2] 66/6 73/24 Von Geusau [2] 66/6 73/24</p>	<p>western [1] 72/22 what [45] 4/9 7/10 9/9 10/15 11/8 11/8 12/6 14/25 17/5 18/12 26/17 26/24 28/12 35/4 35/18 37/10 37/17 38/5 38/17 39/16 42/7 43/4 45/5 46/18 47/8 47/17 48/9 49/12 50/15 52/11 53/15 58/13 61/7 62/23 62/25 63/7 64/11 65/22 67/2 68/9 68/11 68/18 75/2 75/6 76/9 what's [10] 15/6 19/9 38/13 42/24 50/9 55/13 61/14 62/24 63/8 67/5 whatnot [1] 26/2 when [18] 12/16 22/12 26/20 28/2 32/5 42/13 42/15 43/11 43/13 50/22 54/20 59/5 59/7 64/16 64/22 68/23 70/14 75/2 whenever [2] 15/2 18/4 where [3] 4/11 20/19 67/22 whereas [5] 18/11 19/15 24/19 38/11 40/6 WHEREOF [1] 78/18 Whereupon [1] 77/4 whether [7] 19/12 32/8 36/19 48/4 59/20 68/19 71/21 which [19] 5/5 10/5 15/4 24/7 30/5 35/8 44/2 47/9 47/10 50/10 54/17 56/14 64/18 68/3 69/20 72/9 74/23 74/24 75/15 while [3] 37/20 40/5 69/15 who [41] 5/20 6/2 13/20 17/19 20/2 21/4 21/8 21/13 22/6 22/16 22/17 23/5 23/7 23/8 23/15 23/18 23/18 24/20 25/2 25/3 25/16 40/3 41/17 42/17 42/19 44/9 45/14 47/25 48/16 54/11 54/13 55/7 55/21 57/25 58/10 63/23 65/13 68/25 71/17 75/2 75/11 who's [1] 41/21 whole [1] 12/9 whose [2] 48/24 78/10 why [5] 15/8 17/9 27/17 34/20 66/11 will [19] 20/14 20/15 20/17 20/20 21/5 21/9 22/10 23/15 24/4 24/5 24/20 25/10 27/24 33/18 40/6 53/3 56/2 56/5 62/21 wind [8] 20/20 20/21 21/16 21/17 22/16 27/17 40/8 58/18 wise [1] 67/25 within [6] 14/12 23/8 39/6 51/2 61/3 78/8 without [3] 19/14 25/14 39/21 witness [5] 3/11 47/14 78/10 78/13 78/18 word [4] 37/17 46/16 51/7 59/9 words [2] 53/23 63/19 work [26] 5/23 8/24 8/25 10/11 10/12 13/20 21/25 26/4 26/7 26/10 29/25 33/22 44/18 44/24 45/15 45/16 47/15 48/17 50/6 50/17 66/12 66/19 66/25 74/13 74/15 74/22 worked [1] 4/24 working [1] 5/18 world [5] 18/22 32/7 39/17 67/22 68/24 worse [1] 40/6 worst [1] 66/7 would [51] 6/4 9/12 9/12 9/13 9/14 12/2 12/9 12/10 12/10 12/11 12/11 13/6 14/19 14/23 18/2 19/18 19/19 24/17 24/24 26/8 28/8 28/9 36/5 36/6 36/16 37/17 38/7 38/10 39/5 40/11 40/15 41/11 41/13 44/3 45/12 47/14 47/25 50/3 54/5 55/14 56/9 57/9 58/19 65/20 66/3 66/14 67/25 68/25 70/10 72/24 76/3 wouldn't [1] 43/24 writing [1] 49/5 wrong [3] 58/3 64/8 69/12 wrote [1] 58/24</p>
<p>U</p>	<p>W</p>	<p>Y</p>
<p>U.S [2] 2/5 69/2 under [1] 3/8 underlying [1] 67/9 understand [6] 6/12 8/5 9/21 28/6 30/10 44/4 understanding [15] 8/17 8/18 8/23 9/6 9/9 9/23 10/15 11/14 16/15 17/10 17/10 17/14 31/13 32/25 52/4 understood [1] 46/18 UNITED [12] 1/2 1/5 1/18 12/22 16/17 25/8 29/10 37/13 72/17 72/19 72/20 72/25 unknown [1] 38/4 unless [1] 43/25 unlike [1] 61/7 unquote [4] 20/19 34/3 64/14 70/18 until [1] 20/16 up [16] 12/21 20/20 20/21 21/16 21/17 22/16 27/17 31/18 33/7 33/8 33/10 33/15 33/19 40/8 58/10 58/18 upon [1] 12/4 upshot [1] 19/9 urine [1] 9/16 us [8] 32/6 36/23 45/2 46/21 57/7 57/23 62/9 68/2 usages [1] 60/9 use [56] 9/25 12/9 15/15 20/14 20/22 21/4 21/22 22/14 24/16 24/16 24/20 24/22 28/9 28/16 29/6 29/7 29/16 29/20 30/2 30/6 30/11 31/3 31/6 31/12 31/15 32/13 33/16 35/13 36/3 36/12 36/20 39/17 40/13 41/10 41/11 44/6 45/5 45/6 45/9 48/14 49/4 52/7 53/18 55/9 55/10 55/12 55/18 59/9 60/9 62/11 63/15 65/24 68/7 69/17 70/8 75/6 use has [1] 55/18 use/abuse [1] 28/16 used [13] 10/25 27/2 34/5 35/21 40/17 41/18 41/20 42/2 42/17 42/19 44/18 55/23 69/24 user [3] 60/22 67/15 67/16 user's [1] 61/22 users [27] 9/20 22/23 23/4 23/18 24/22 39/13 39/17 39/21 40/3 42/14 42/14 42/17 42/19 43/2 43/3 44/8 44/25 57/25 58/10 58/14 58/17 60/2 60/19 63/12 65/17 66/7 75/11 uses [2] 21/15 59/22 using [13] 10/5 13/22 20/21 21/17 21/18 33/17 36/10 39/13 55/24 58/6 62/6 62/19 66/21 usually [3] 27/2 68/7 68/9 utility [1] 65/11 utterly [1] 47/12</p>	<p>want [13] 3/19 7/9 19/17 20/14 28/13 29/11 37/15 46/16 49/8 56/12 57/4 64/14 65/13 wanted [1] 62/20 Warning [1] 31/25 warrant [2] 75/9 75/21 was [80] 3/12 4/9 4/11 4/20 9/9 9/11 9/23 10/13 10/15 10/16 10/17 10/21 10/25 12/13 13/19 13/25 14/2 14/4 14/12 14/23 15/25 16/2 16/16 25/24 26/7 26/10 27/23 29/16 30/8 30/8 30/20 30/24 32/22 33/20 37/8 45/2 45/16 45/19 45/21 45/25 45/25 46/6 46/13 47/2 47/3 47/3 47/16 47/18 48/20 49/7 49/16 50/4 50/6 50/16 51/5 54/13 54/24 54/25 54/25 55/3 56/18 57/12 57/21 57/24 58/6 58/6 59/3 59/9 59/10 59/22 60/15 60/17 60/18 61/7 64/18 66/22 74/2 74/14 74/22 78/11 washup [1] 40/12 wasn't [3] 11/2 44/23 73/4 wave [1] 12/12 way [11] 9/15 17/22 19/7 21/11 31/22 33/16 34/11 39/5 64/21 67/14 78/17 ways [2] 35/24 36/6 we [87] we'll [3] 8/15 18/8 20/9 we're [12] 3/4 7/10 36/10 36/15 41/10 43/4 51/8 53/23 65/7 65/22 67/22 68/3 we've [2] 9/17 63/21 weak [1] 66/11 weakness [3] 37/21 37/21 67/9 wears [1] 20/12 well [35] 5/8 5/10 6/6 8/2 8/20 9/11 12/8 16/3 18/8 18/15 18/18 20/12 21/24 25/19 29/8 29/24 33/21 35/20 37/10 39/4 40/8 49/2 49/20 53/17 54/8 55/6 56/6 58/4 63/11 64/9 64/16 72/13 73/23 74/17 75/10 went [2] 31/18 64/21 were [26] 4/15 9/23 12/3 12/8 14/10 22/7 23/18 31/3 33/17 38/8 38/12 42/7 42/10 45/18 48/16 54/14 57/7 57/17 59/6 59/7 61/19 64/16 66/12 66/25 70/7 73/22</p>	<p>Yablonski [1] 69/15 Yablonski-Alter [1] 69/15 yeah [13] 10/19 14/15 16/12 31/25 32/19 38/22 56/21 57/12 66/10 69/13 71/23 73/25 73/25 year [13] 12/21 12/24 14/3 29/22 29/22 30/6</p>

Y

year... [7] 30/7 30/19 30/19 31/8 33/12 47/17
57/21
years [6] 26/8 30/3 31/18 48/14 51/16 65/5
yes [42] 3/9 4/3 4/5 4/8 4/17 5/13 7/14 7/17
7/21 8/3 10/3 11/13 13/18 14/21 14/25 16/19
17/4 18/6 25/8 28/18 28/23 31/5 32/14 33/4
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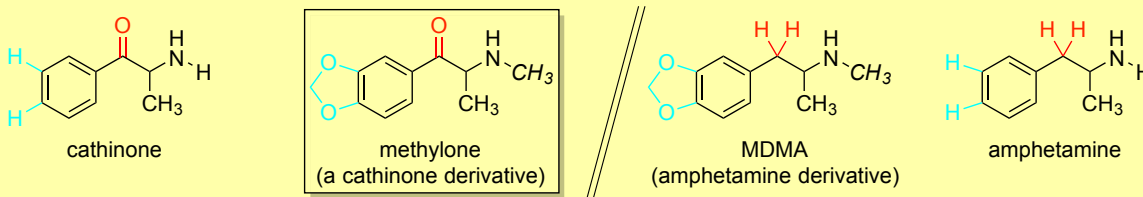
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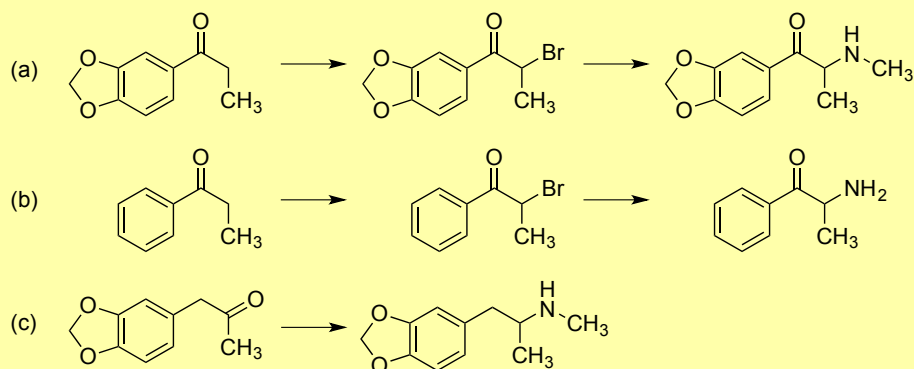
Appendix C

DECLARATION OF Dr. GREGORY B. DUDLEY, Ph.D.

1. I am over the age of 21.
2. I have personal knowledge of the matters contained within this Declaration.
3. I am an independent consultant specializing in organic chemistry and related fields.
4. I am an Associate Professor and Associate Chair in the Department of Chemistry and Biochemistry at Florida State University.
5. I received a B.A. degree in chemistry from Florida State University in 1995 and a PhD in organic chemistry from Massachusetts Institute of Technology in 2000. I was a postdoctoral research fellow in the Molecular Pharmacology and Chemistry program at the Memorial Sloan-Kettering Cancer Center in New York from 2000 until 2002.
6. I am an organic chemist with professional expertise in synthetic chemistry, chemical structure, molecular interactions, and structure-activity relationships. My primary research focus is on the synthesis of drugs and drug-like compounds. I have published and lectured extensively in these areas, as reflected in my CV, which is attached and referenced in full as Exhibit 1.
7. I have reviewed the chemical structures of methylone, cathinone, and methylenedioxymethamphetamine (MDMA) for the purpose of determining whether methylone is more similar to cathinone or to MDMA.
8. This Declaration is true and accurate to the best of my knowledge and information.
9. It is my expert scientific opinion that methylone more similar in chemical structure to cathinone than it is to MDMA.
10. Simple two-dimensional and color-coded representations of the chemical structures in question are provided in the graphic below.

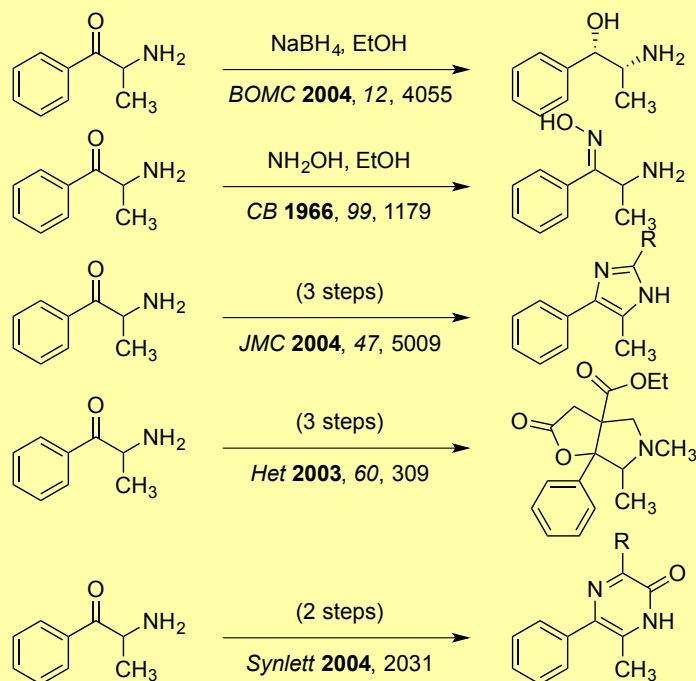


11. Structurally, methylone is classified as a “cathinone” to indicate that methylone includes the core structure of the substance found naturally in the khat plant, cathinone.
12. In contrast, methylenedioxyamphetamine (MDMA) is classified as an “amphetamine” because MDMA has the amphetamine core structure.
13. MDMA differs from amphetamine in the same way that methylone differs from cathinone: methyl group on nitrogen (in *italics*) and methylenedioxy fused to the aromatic ring (highlighted in light blue).
14. What distinguishes methylone from MDMA also distinguishes cathinone from amphetamine: the presence or absence of the ketone (highlighted in red).
15. Methylone is a cathinone, so the better comparison is to cathinone rather than the MDMA, which is an amphetamine.
16. Representative pathways for the chemical synthesis of (a) methylone, (b) cathinone, and (c) MDMA are provided in the graphic below.



17. Methylone can be formally described as a chemical derivative of cathinone.
18. Although methylone cannot easily be prepared directly from cathinone, synthesis of methylone and cathinone follow analogous routes (a and b).
19. The syntheses of cathinone and methylone follow similar paths, whereas the synthesis of MDMA is different.
20. The reason that the synthesis of MDMA is different is because *MDMA is an amphetamine, not a cathinone*.
21. Amphetamines like MDMA lack the ketone (C=O) functionality of the cathinones, so the synthesis is different.

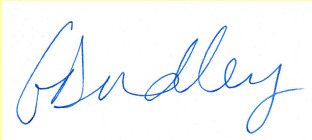
22. The ketone that differentiates cathinones from amphetamines is also responsible for many of the chemical properties of cathinones, as described below.
23. Examples of five chemical transformations of cathinone are presented in the graphic below.




24. In my expert opinion, each of these five transformations would be similarly applicable to methylone but not to MDMA.
25. I did not find any reactions that in my expert opinion would be applicable to MDMA and to methylone but not to cathinone.
26. The chemical reactivity of cathinones and amphetamines is different.
27. Cathinones and amphetamines both have amines (nitrogen groups), but only cathinones have the ketone ($\text{C}=\text{O}$) group, which opens up a much larger set of chemistries.
28. Therefore, I conclude that methylone is more similar in chemical structure to cathinone than it is to MDMA. Methylone is a cathinone. Its synthesis and reactivity patterns are those of cathinones, not amphetamines like MDMA.
29. My analysis and opinions regarding the chemical structures and chemical reactivities of methylone, cathinone, and MDMA would be accepted by the scientific community.

I declare under penalty of perjury under the laws of the State of Florida that the foregoing is true and correct.

Executed on June 20, 2014 at Tallahassee, Florida.

A handwritten signature in blue ink that reads "Dudley". The signature is written in a cursive style with a large initial 'D'.

GREGORY B. DUDLEY, Ph.D.

A white rectangular redaction box covering the text below the signature line.

Appendix D

DECLARATION OF CHARLES S. GROB, M.D.

I, Charles S. Grob, M.D., declare as follows:

- 1) I am a physician licensed to practice in the State of California since 1980. I make this declaration based upon my personal knowledge of the following facts and if called as a witness I could and would testify to the facts set forth herein.
- 2) I am a physician specializing in psychiatry as well as child and adolescent psychiatry. I am certified by the American Board of Psychiatry and Neurology in both General Psychiatry and Child and Adolescent Psychiatry. In 1975 I received my B.S. degree from Columbia University. In 1979 I received my M.D. degree from the State University of New York, Downstate Medical Center, in Brooklyn, N.Y. I completed my medical internship in 1980 at Pacific Medical Center in San Francisco, CA. I completed my general psychiatry residency in 1982 at Cedars-Sinai Medical Center in Los Angeles, CA. I completed my child and adolescent psychiatry fellowship in 1984 at The Johns Hopkins Hospital in Baltimore, MD. I was on the full-time faculty in the Departments of Psychiatry and Pediatrics at The Johns Hopkins Hospital from 1984 – 1987 and the Department of Psychiatry at the University of California, Irvine, from 1987 – 1993.
- 3) From 1993 to the present I have been on the full-time faculty of Harbor-UCLA Medical Center in Torrance, CA. During this time I have been the Director of the Division of Child and Adolescent Psychiatry. I am currently a Professor of Psychiatry and Pediatrics at the UCLA School of Medicine
- 4) Over the last twenty-five years I have developed as an area of research expertise the study of hallucinogens and their relation to the fields of medicine and psychiatry. I have published numerous review and original research articles in the professional literature on this topic. In the 1990s I conducted the first FDA approved research investigation with the drug 3,4-methylenedioxymethamphetamine (MDMA), a Phase 1 study of the range of physiological and psychological effects in adult normal volunteer subjects. I am currently conducting an FDA approved investigation of the use of an MDMA treatment model in adults diagnosed on the autism spectrum who have comorbid social anxiety.
- 5) I have also conducted human research on the range of effects of the Amazonian plant hallucinogen decoction, ayahuasca, as well as a clinical

treatment study of psilocybin (the active alkaloid in hallucinogenic mushrooms) in patients with advanced-stage cancer and severe existential anxiety. Our findings for this study were published in the *Archives of General Psychiatry* in 2011

- 6) I have been asked to comment on the drugs methylone and MDMA, in relation to criminal court sentencing guidelines.
- 7) Methylone is 3,4-methylenedioxymethcathinone, a synthetic cathinone derivative of the khat plant (*Catha edulis*). Khat has a natural habitat that covers much of the Horn of Africa and the Arabian Peninsula. Chewing the leaves of the khat plant for its psychostimulant effects has been documented within its area of cultivation for several hundred years, and in all likelihood dates to antiquity. It is considered to be relatively well-tolerated and is culturally accepted. There are believed to be currently ten million daily khat users worldwide, though predominantly in east Africa and the Arabian Peninsula.
- 8) Over the last several years interest has developed in methylone, along with mephedrone (4-methylmethcathinone) and MDPV (3,4-methylenedioxypropylvalerone), which have been collectively referred to informally by users and by the media as “bath salts”. Their use in the United States did not emerge until 2010, although they were known a few years earlier in western Europe. By late 2011 they were officially classified in the U.S. as Schedule 1 drugs, reflecting media sensationalizing coverage of what was considered to be a new and emerging drug trend. Unfortunately, Schedule 1 status severely restricts human subject research and complicates objective assessment of the range of effects of these compounds. Schedule 1 classification also impedes controlled investigation of potential therapeutic applications, seriously limiting the development of new and potentially valuable medicinal agents. Consequently, little clinical research has been conducted and our knowledge of the range of effects of these drugs remains limited.
- 9) While mephedrone was first synthesized in 1929 and MDPV in 1967, methylone was not synthesized until the 1990s, by chemists Alexander Shulgin and Peyton Jacob, who in 1996 patented the compound as an antidepressant and anti-Parkinsonian agent. No formal investigations were conducted, however, owing first to lack of funding and subsequently to the emergence of the recreational “bath salt” phenomenon in the U.S. Of note, however, is the chemical structural similarity of the approved medication bupropion (sold under the brand names *Wellbutrin* as an antidepressant and as treatment for ADHD, and

Zyban as a smoking cessation drug) to methylone. While not considered to be an abused drug, bupropion will substitute for cocaine and amphetamine in pre-clinical laboratory studies conducted in animal models.

- 10) While most individuals who ingest synthetic cathinones tolerate them without evident deleterious effect, and anecdotal accounts reflect the experience of some users who believe that this class of drugs may have therapeutic effects, there have been a small number of adverse outcomes reported in the literature. Most of these deleterious effects, however, appear to occur in individuals who had taken mephedrone or MDPV, but not methylone. In many of these cases there were also a variety of mitigating factors that increased the likelihood of problematic outcome, including polydrug use (taking additional drugs and alcohol along with the synthetic cathinones), excessive dosages and pre-existing medical and/or psychiatric conditions. Furthermore, the role of the media in creating false impressions cannot be discounted, an example being the May, 2012 homicide in Miami, Florida, known as the “Miami cannibal attack”, and widely attributed in the press to “bath salt” ingestion. Subsequent investigation, however, identified that the only drug to test positive on toxicology in the severely mentally disturbed assailant was marijuana. While no synthetic cathinone was apparently involved in this tragic case, there remains the lingering public perception that “bath salts” were the cause. The impact, consequently, of such media sensationalizing and distortion on public perception and on sentencing guidelines are unfortunately not insignificant.
- 11) In both the United States and Europe the predominant compounds identified in analyzed samples of “bath salts” turn out to be mephedrone and MDPV. In the U.S, as per recent data provided by the DEA Office of Diversion Control, only about ¼ of such analyses have identified methylone. There are differences between the different “bath salts” and when compared to other psychostimulants. Pre-clinical laboratory studies have established that MDPV has far greater similarities to cocaine’s effects on the monoamine dopamine than does methylone. Furthermore, mephedrone induced much higher levels of drug self-administration than did methylone. And unlike cocaine or methamphetamine, methylone did not lead to escalating drug intake or increased reinforcer efficacy. Indeed, methylone, on the basis of such laboratory drug discrimination studies, is considered to have relatively lower potential for abuse and compulsive use than the prototypical psychostimulants, cocaine and methamphetamine. Of related significance is that the prescription medication, bupropion, in animal models trained to discriminate between different drugs, will substitute for cocaine and methamphetamine, while methylone will not substitute for cocaine and methamphetamine.

- 12) Methylone is considered to have comparatively low toxicity to central monamine systems when taken alone. As such, some investigators have considered it to be a potentially useful alternative clinically for the treatment of refractory, or treatment resistant, depression or attention deficit hyperactivity disorder (ADHD). While associated with a range of adverse effects, most reported cases were of individuals who had engaged in polysubstance abuse. Ex. 1, N.Y. Hrg. Tr. at 382 (Hanson). Modest dosages of methylone taken alone, in the absence of other drugs, does not appear to be particularly hazardous to health. While a handful of deaths have been reported, according to data provided by the DEA, as of 2013 only three fatalities had been associated with methylone, and these were likely in the context of polysubstance abuse and excessive dosages.
- 13) Most individuals who have taken methylone, at modest dosages, report a mild, easily controlled altered state of consciousness. Indeed, a methylone high is characterized by its mild effects on sensorium, increased empathy towards self and others and perceived potential (albeit as yet formally unexplored) for therapeutic application in appropriate settings.
- 14) Compared to the prototype psychostimulant, cocaine, methylone (when taken at appropriate dose and in the absence of polysubstance use), on the basis of available clinical data, is much milder, less likely to be habit forming or addictive, far less likely to be associated with violent behavior and implicated in far fewer fatalities. Apart from alcohol, cocaine is associated with more Emergency Department visits in the United States than any other drug of abuse. In 2009, approximately 425,000 ER visits in the U.S. were associated with cocaine use and in 2011, over 500,000 Emergency Department visits were reported to be related to cocaine use. Government data bases of ER visits for methylone, however, are very limited, owing to its relatively recent emergence as a drug of interest and the temporal lag in reporting accumulated data. The most recent data for Emergency Department visits and associated drug use, from 2011, does not include mention of methylone or the other so-called "bath salts". While there have undoubtedly been such cases over the past few years, it is likely that cases of moderate dose methylone, used in the absence of other drugs, comprise only a miniscule percentage of the overall number of drug related emergencies.
- 15) As Director of a Division of Child and Adolescent Psychiatry at a very large public sector academic medical center for the past twenty-one years, where I am responsible for the clinical oversight of over 1,000

- patients annually in outpatient and psychiatric emergency room settings, I have been informed of only a very small number of patients who had presented with methylone or other synthetic cathinone abuse. This contrasts significantly with frequent reports of cocaine and methamphetamine use that have commonly been identified among adolescents and adults undergoing evaluation in our clinical settings.
- 16) Regarding the drug MDMA (3,4-methylenedioxymethamphetamine), far more information is available than with methylone,
 - 17) given its relatively long presence as both a recreational drug and as a potential therapeutic agent that has in fact been examined in human research studies. In regards to the purpose of this declaration, to contrast the range of effects of MDMA with that of cocaine, for purposes of sentencing guidelines, the ruling of Judge W.H. Pauley in the McCarthy versus United States decision, in 2011, is quite relevant. In his ruling, Judge Pauley accurately determined that MDMA causes significantly less risk of injury to users than cocaine, and consequently that its illicit use should be subject to a lesser degree of punishment as per sentencing guidelines, compared to cocaine.
 - 18) In Judge Pauley's ruling he provides Emergency Department data from 2007 for cocaine, which constituted over one-half million total ER visits (almost 30% of all drug or alcohol related visits), and MDMA, which comprised less than 13,000 visits and 0.7% of total ER drug and alcohol related episodes.
 - 19) In regards to relative risks to health and safety, cocaine is a far more dangerous drug than MDMA. Cocaine has long been identified as a drug with high addiction potential, whereas MDMA does not cause physiological addiction, though it is capable of creating states of psychological dependence in a minority of users. Cocaine is also far more likely to precipitate episodes of violence and agitation than MDMA, which is associated with facilitating empathic and expansive states of consciousness, and has in some circles acquired the informal name of the "love drug". While MDMA is certainly not without risk, and has been identified in fatal outcomes, it is well established that effective safety parameters do exist when proper attention is given to set and setting. Most adverse outcomes with MDMA occur in the context of excessive dosing, concomitant polysubstance abuse, underlying medical and psychiatric vulnerabilities and high risk settings (eg. so-called "rave" events, which are often associated with prolonged exercise [dancing], poor ventilation, high ambient temperatures and lack of fluid replacement, which can lead to very dangerous, albeit rare, cases of malignant hyperthermia). Most users of MDMA consume the drug on limited occasions. Daily use of MDMA, unlike cocaine, is extremely rare.

Most individuals who self-administer MDMA do so only on an occasional basis, and over time appear to self-limit their use. A major problem with MDMA use, and likely responsible for a significant percentage of adverse outcomes, is the high risk of drug substitution. Marketed as “ecstasy”, surveys have identified that upwards to half of these drugs contain psychoactive substances other than MDMA. In fact, a number of deaths attributed to “ecstasy” appear to have been caused not by MDMA, which was not present on toxicological analyses, but rather PMA (paramethoxyamphetamine), considered to be one of the most potent and dangerous amphetamines known to man. Nevertheless, because of widespread misinformation and confusion, often propagated by sensationalized media coverage, these adverse “ecstasy” outcomes have often been mistakenly attributed to MDMA.

- 20) From the late 1980s to the early 2000s, substantial media coverage as well as expenditure of considerable federal research funding focused on the supposed risk of MDMA induced neurotoxicity. Judge Pauley, in his 2011 opinion, accurately identifies that such concerns have often been exaggerated. While excessive use of what is often a poor quality product, taken with other drugs and alcohol and under adverse conditions by individuals with significant underlying vulnerability, may clearly lead to impaired neuropsychological and psychiatric status, it is equally apparent that modest dosages taken on only an occasional or single time basis, in the absence of other drugs or alcohol, and under optimal conditions by individuals with relatively good psychiatric and medical health, do not appear to be associated with any clinically significant decrement of function. I have documented the serious methodological flaws along with misleading data interpretations present in some of the high profile MDMA neurotoxicity literature in several reviews I have published in psychiatric, neuroscience and drug abuse journals and textbooks over the last fifteen years. In recent years, however, there appears to be growing recognition that the fears of MDMA induced brain damage have been grossly overstated and consequently there has evolved considerably reduced media coverage of this issue.
- 21) Indeed, much of the preclinical laboratory evidence of neurotoxicity has been from small animal studies (usually with rats) where very high dosages of MDMA were injected into the animal, sometimes twice daily over multiple successive days, whereas recreational human users take MDMA orally and never inject the drug, virtually never take MDMA on successive days and almost always self-administer MDMA at least a week or often much longer apart and proportionally use far smaller dosages than the animals are injected with.

- 22) While recreational use has lessened over the past decade, interest has grown in MDMA's potential as an adjunct to psychiatric treatment, particularly in disorders that have proved to be refractory, or non-responsive, to conventional treatment. Formally approved studies have recently been conducted on patients with chronic, treatment-resistant post-traumatic stress disorder (PTSD). Published results indicate that while very good safety parameters were maintained during treatment, with no evident injury to subjects, treatment outcome was frequently excellent, with complete resolution of disabling symptoms in many of the individuals treated. Before its emergence as a popular recreational drug in the late 1980s and early 1990s, MDMA was considered to be a highly promising compound, when implemented in an optimally constructed treatment model, with potential application to a variety of difficult to treat psychiatric conditions. Regrettably, with the surging recreational use of "ecstasy", formal and approved clinical research with MDMA had to be put on hold. At the present time, however, with the growing appreciation of the genuine risk to benefit ratio of MDMA, it is now possible for properly accredited investigators to receive federal, state and local sanction to conduct research into MDMA's potential as a safe and efficacious treatment. As indicated above, my research group at Harbor-UCLA Medical Center and the Los Angeles BioMedical Research Institute is currently conducting an FDA approved investigation of the use of an MDMA treatment model with adults on the autism spectrum who have social anxiety.
- 23) Over the last twenty-five years I have published in the professional literature a number of research and review articles on MDMA. Some, though not all, of my publications are referenced in this document as follows:
- 24) **Grob, C.S.**, Bravo, G. and Walsh, R.: Second Thoughts on 3,4 - Methylendioxyamphetamine (MDMA) Neurotoxicity, Archives of General Psychiatry, 47:288-289, 1990.
- 25) Liester, M.B., **Grob, C.S.**, Bravo, G.L. and Walsh, R.N.: Phenomenology and Sequelae of 3,4- Methylendioxyamphetamine Use, Journal of Nervous and Mental Disease, 180:345-352, 1992.
- 26) **Grob, C.S.**, Bravo, G.L., Walsh, R.N. and Liester, M.B.: The MDMA-neurotoxicity controversy: Implications for clinical research with novel psychoactive drugs, Journal of Nervous and Mental Disease, 180:355-356, 1992.

- 27) **Grob, C.S.**, Poland, R.E, Chang, L. and Ernst, T: Psychobiologic effects of 3,4-methylenedioxyamphetamine (MDMA) in humans: methodological considerations and preliminary data, *Behavioural Brain Research*, 73:103-107, 1996.
- 28) **Grob, C.S.** and Poland, R.E: MDMA. In J.H. Lowinson, P. Ruiz, R.B. Millman and J.G. Langrod (Eds.), Substance Abuse: A Comprehensive Textbook, 3rd Edition, Baltimore: Williams and Wilkins, pp. 269-275, 1997.
- 29) **Grob, C.S.:** MDMA research: preliminary investigations with human subjects. *International Journal of Drug Policy* 9:119-124, 1998.
- 30) **Grob, C.S.:** Psychedelic drug research: recent developments with MDMA and ayahuasca, in R. Verres, H. Leuner and A. Dittrich (Eds.), Welten Des Bewusstseins, Berlin, Verlag fur Wissenschaft und Bildung, pp. 93-109. 1998.
- 31) Chang, L, Ernst, T.M, **Grob, C.S.** and Poland R.E: Proton magnetic resonance Spectroscopy in 3,4-methylenedioxyamphetamine (MDMA or "ecstasy") users. *Journal of Magnetic Resonance Imaging* 10:521-526, 1999.
- 32) Chang, L., **Grob, C.S.**, Itti, L., Mishkin, F., Ernst, T., and Poland, R.E: Effect of ecstasy [3,4- Methylenedioxy-methamphetamine (MDMA)] on cerebral blood flow: A co-registered SPECT and MRI study. *Psychiatry Research: Neuroimaging Section* 98:15-28, 2000.
- 33) **Grob, C.S.:** Deconstructing ecstasy: The politics of MDMA research. *Addiction Research* 8:549-588, 2000.
- 34) **Grob, C.S.** Is U.S. drug policy on ecstasy scientifically justified? *Journal of Addiction and Mental Health* 5(2):17, 2002.
- 35) **Grob, C.S.** The politics of ecstasy. *Journal of Psychoactive Drugs* 34:143-144, 2002.
- 36) Cole, J, Sumnall, H. and **Grob, C.S.** Sorted: Ecstasy facts and fiction. *The Psychologist* 15:464-467, 2002.
- 37) Cole, J, Sumnall, H. and **Grob, C.S.** Where are the casualties? *The Psychologist* 15:474, 2002.
- 38) Back-Madruga, C, Boone, K.B, Chang, L, **Grob, C.S.**, Lee, A, Nations, H. and Poland,R.E.Neuropsychological effectsof3,4-methylenedioxyamphetamine

(MDMA or ecstasy) in recreational users. *Clinical Neuropsychology* 17:446-459, 2003.

- 39) **Grob, C.S.** and Poland, R.E: MDMA: in J.H. Lowinson, P. Ruiz, R.B. Millman and J.G. Langrod (Eds.), Substance Abuse: A Comprehensive Textbook, 4th Edition, Philadelphia: Williams and Wilkins, pp. 274-286, 2005.
- 40) **Grob, C.S.** The enigma of ecstasy: implications for youth and society. *Adolescent Psychiatry* 29:97-117, 2005.
- 41) Danforth, A.L. and **Grob, C.S.** Ecstasy: in G.L. Fisher and N.A. Roget (Eds.), Encyclopedia of Substance Abuse Prevention, Treatment and Recovery. London, U.K, Sage Publishers, pp. 352-354, 2009.
- 42) **Grob, C.S.** and Dobkin de Rios, M. Hallucinogens and related compounds: in R. Rosner (Ed.), Clinical Handbook of Adolescent Addiction. New York, Wiley-Blackwell, pp. 213- 223, 2013.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Executed on June 21, 2014 at Irvine, California.

CHARLES S. GROB, M.D.

Appendix E

EXHIBIT A

EXHIBIT A

DECLARATION OF CHARLES S. GROB, M.D.

I, Charles S. Grob, M.D., declare as follows:

- 1) I am a physician licensed to practice in the State of California since 1980. I make this declaration based upon my personal knowledge of the following facts and if called as a witness I could and would testify to the facts set forth herein.
- 2) I am a physician specializing in psychiatry as well as child and adolescent psychiatry. I am certified by the American Board of Psychiatry and Neurology in both General Psychiatry and Child and Adolescent Psychiatry. In 1975 I received my B.S. degree from Columbia University. In 1979 I received my M.D. degree from the State University of New York, Downstate Medical Center, in Brooklyn, N.Y. I completed my medical internship in 1980 at Pacific Medical Center in San Francisco, CA. I completed my general psychiatry residency in 1982 at Cedars-Sinai Medical Center in Los Angeles, CA. I completed my child and adolescent psychiatry fellowship in 1984 at The Johns Hopkins Hospital in Baltimore, MD. I was on the full-time faculty in the Departments of Psychiatry and Pediatrics at The Johns Hopkins Hospital from 1984 – 1987 and the Department of Psychiatry at the University of California, Irvine, from 1987 – 1993.
- 3) From 1993 to the present I have been on the full-time faculty of Harbor-UCLA Medical Center in Torrance, CA. During this time I have been the Director of the Division of Child and Adolescent Psychiatry. I am currently a Professor of Psychiatry and Pediatrics at the UCLA School of Medicine.
- 4) Over the last twenty-five years I have developed as an area of research expertise the study of hallucinogens and their relation to the fields of medicine and psychiatry. I have published numerous review and original research articles in the professional literature on this topic. In the 1990s I conducted the first FDA approved research investigation with the drug 3,4-methylenedioxymethamphetamine (MDMA), a Phase 1 study of the range of physiological and psychological effects in adult normal volunteer subjects. I am currently conducting an FDA approved investigation of the use of an MDMA treatment model in adults diagnosed on the autism spectrum who have comorbid social anxiety.
- 5) I have also conducted human research on the range of effects of the Amazonian plant hallucinogen decoction, ayahuasca, as well as a clinical treatment study of psilocybin (the active alkaloid in hallucinogenic mushrooms) in patients with advanced-stage cancer and severe existential anxiety. Our findings for this study were published in the *Archives of General Psychiatry* in 2011.
- 6) I have been asked to comment on the drugs methylone and MDMA, in relation to criminal court sentencing guidelines.

- 7) Methylone is 3,4-methylenedioxymethcathinone, a synthetic cathinone derivative of the khat plant (*Catha edulis*). Khat has a natural habitat that covers much of the Horn of Africa and the Arabian Peninsula. Chewing the leaves of the khat plant for its psychostimulant effects has been documented within its area of cultivation for several hundred years, and in all likelihood dates to antiquity. It is considered to be relatively well-tolerated and is culturally accepted. There are believed to be currently ten million daily khat users worldwide, though predominantly in east Africa and the Arabian Peninsula.
- 8) Over the last several years interest has developed in methylone, along with mephedrone (4-methylmethcathinone) and MDPV (3,4-methylenedioxypropylone), which have been collectively referred to informally by users and by the media as “bath salts”. Their use in the United States did not emerge until 2010, although they were known a few years earlier in western Europe. By late 2011 they were officially classified in the U.S. as Schedule 1 drugs, reflecting media sensationalizing coverage of what was considered to be a new and emerging drug trend. Unfortunately, Schedule 1 status severely restricts human subject research and complicates objective assessment of the range of effects of these compounds. Schedule 1 classification also impedes controlled investigation of potential therapeutic applications, seriously limiting the development of new and potentially valuable medicinal agents. Consequently, little clinical research has been conducted and our knowledge of the range of effects of these drugs remains limited.
- 9) While mephedrone was first synthesized in 1929 and MDPV in 1967, methylone was not synthesized until the 1990s, by chemists Alexander Shulgin and Peyton Jacob, who in 1996 patented the compound as an antidepressant and anti-Parkinsonian agent. No formal investigations were conducted, however, owing first to lack of funding and subsequently to the emergence of the recreational “bath salt” phenomenon in the U.S. Of note, however, is the chemical structural similarity of the approved medication bupropion (sold under the brand names *Wellbutrin* as an antidepressant and as treatment for ADHD, and *Zyban* as a smoking cessation drug) to methylone. While not considered to be an abused drug, bupropion will substitute for cocaine and amphetamine in pre-clinical laboratory studies conducted in animal models.
- 10) While most individuals who ingest synthetic cathinones tolerate them without evident deleterious effect, and anecdotal accounts reflect the experience of some users who believe that this class of drugs may have therapeutic effects, there have been a small number of adverse outcomes reported in the literature. Most of these deleterious effects, however, appear to occur in individuals who had taken mephedrone or MDPV, but not methylone. In many of these cases there were also a variety of mitigating factors that increased the likelihood of problematic

outcome, including polydrug use (taking additional drugs and alcohol along with the synthetic cathinones), excessive dosages and pre-existing medical and/or psychiatric conditions. Furthermore, the role of the media in creating false impressions cannot be discounted, an example being the May, 2012 homicide in Miami, Florida, known as the “Miami cannibal attack”, and widely attributed in the press to “bath salt” ingestion. Subsequent investigation, however, identified that the only drug to test positive on toxicology in the severely mentally disturbed assailant was marijuana. While no synthetic cathinone was apparently involved in this tragic case, there remains the lingering public perception that “bath salts” were the cause. The impact, consequently, of such media sensationalizing and distortion on public perception and on sentencing guidelines are unfortunately not insignificant.

- 11) In both the United States and Europe the predominant compounds identified in analyzed samples of “bath salts” turn out to be mephedrone and MDPV. In the U.S, as per recent data provided by the DEA Office of Diversion Control, only about ¼ of such analyses have identified methylone. There are differences between the different “bath salts” and when compared to other psychostimulants. Pre-clinical laboratory studies have established that MDPV has far greater similarities to cocaine’s effects on the monoamine dopamine than does methylone. Furthermore, mephedrone induced much higher levels of drug self-administration than did methylone. And unlike cocaine or methamphetamine, methylone did not lead to escalating drug intake or increased reinforcer efficacy. Indeed, methylone, on the basis of such laboratory drug discrimination studies, is considered to have relatively lower potential for abuse and compulsive use than the prototypical psychostimulants, cocaine and methamphetamine. Of related significance is that the prescription medication, bupropion, in animal models trained to discriminate between different drugs, will substitute for cocaine and methamphetamine, while methylone will not substitute for cocaine and methamphetamine.
- 12) Methylone is considered to have comparatively low toxicity to central monoamine systems when taken alone. As such, some investigators have considered it to be a potentially useful alternative clinically for the treatment of refractory, or treatment resistant, depression or attention deficit hyperactivity disorder (ADHD). While associated with a range of adverse effects, most reported cases were of individuals who had engaged in polysubstance abuse. Modest dosages of methylone taken alone, in the absence of other drugs, does not appear to be particularly hazardous to health. While a handful of deaths have been reported, according to data provided by the DEA, as of 2013 only three fatalities had been associated with methylone, and these were likely in the context of polysubstance abuse and excessive dosages.
- 13) Most individuals who have taken methylone, at modest dosages, report a mild, easily controlled altered state of consciousness. Indeed, a

methylone high is characterized by its mild effects on sensorium, increased empathy towards self and others and perceived potential (albeit as yet formally unexplored) for therapeutic application in appropriate settings.

- 14) Compared to the prototype psychostimulant, cocaine, methylone (when taken at appropriate dose and in the absence of polysubstance use), on the basis of available clinical data, is much milder, less likely to be habit forming or addictive, far less likely to be associated with violent behavior and implicated in far fewer fatalities. Apart from alcohol, cocaine is associated with more Emergency Department visits in the United States than any other drug of abuse. In 2009, approximately 425,000 ER visits in the U.S. were associated with cocaine use and in 2011, over 500,000 Emergency Department visits were reported to be related to cocaine use. Government data bases of ER visits for methylone, however, are very limited, owing to its relatively recent emergence as a drug of interest and the temporal lag in reporting accumulated data. The most recent data for Emergency Department visits and associated drug use, from 2011, does not include mention of methylone or the other so-called "bath salts". While there have undoubtedly been such cases over the past few years, it is likely that cases of moderate dose methylone, used in the absence of other drugs, comprise only a miniscule percentage of the overall number of drug related emergencies.
- 15) As Director of a Division of Child and Adolescent Psychiatry at a very large public sector academic medical center for the past twenty-one years, where I am responsible for the clinical oversight of over 1,000 patients annually in outpatient and psychiatric emergency room settings, I have been informed of only a very small number of patients who had presented with methylone or other synthetic cathinone abuse. This contrasts significantly with frequent reports of cocaine and methamphetamine use that have commonly been identified among adolescents and adults undergoing evaluation in our clinical settings.
- 16) Regarding the drug MDMA (3,4-methylenedioxymethamphetamine), far more information is available than with methylone, given its relatively long presence as both a recreational drug and as a potential therapeutic agent that has in fact been examined in human research studies. In regards to the purpose of this declaration, to contrast the range of effects of MDMA with that of cocaine, for purposes of sentencing guidelines, the ruling of Judge W.H. Pauley in the McCarthy versus United States decision, in 2011, is quite relevant. In his ruling, Judge Pauley accurately determined that MDMA causes significantly less risk of injury to users than cocaine, and consequently that its illicit use should be subject to a lesser degree of punishment as per sentencing guidelines, compared to cocaine.
- 17) In Judge Pauley's ruling he provides Emergency Department data from 2007 for cocaine, which constituted over one-half million total ER visits

(almost 30% of all drug or alcohol related visits), and MDMA, which comprised less than 13,000 visits and 0.7% of total ER drug and alcohol related episodes.

- 18) In regards to relative risks to health and safety, cocaine is a far more dangerous drug than MDMA. Cocaine has long been identified as a drug with high addiction potential, whereas MDMA does not cause physiological addiction, though it is capable of creating states of psychological dependence in a minority of users. Cocaine is also far more likely to precipitate episodes of violence and agitation than MDMA, which is associated with facilitating empathic and expansive states of consciousness, and has in some circles acquired the informal name of the “love drug”. While MDMA is certainly not without risk, and has been identified in fatal outcomes, it is well established that effective safety parameters do exist when proper attention is given to set and setting. Most adverse outcomes with MDMA occur in the context of excessive dosing, concomitant polysubstance abuse, underlying medical and psychiatric vulnerabilities and high risk settings (eg. so-called “rave” events, which are often associated with prolonged exercise [dancing], poor ventilation, high ambient temperatures and lack of fluid replacement, which can lead to very dangerous, albeit rare, cases of malignant hyperthermia). Most users of MDMA consume the drug on limited occasions. Daily use of MDMA, unlike cocaine, is extremely rare. Most individuals who self-administer MDMA do so only on an occasional basis, and over time appear to self-limit their use. A major problem with MDMA use, and likely responsible for a significant percentage of adverse outcomes, is the high risk of drug substitution. Marketed as “ecstasy”, surveys have identified that upwards to half of these drugs contain psychoactive substances other than MDMA. In fact, a number of deaths attributed to “ecstasy” appear to have been caused not by MDMA, which was not present on toxicological analyses, but rather PMA (paramethoxyamphetamine), considered to be one of the most potent and dangerous amphetamines known to man. Nevertheless, because of widespread misinformation and confusion, often propagated by sensationalized media coverage, these adverse “ecstasy” outcomes have often been mistakenly attributed to MDMA.
- 19) From the late 1980s to the early 2000s, substantial media coverage as well as expenditure of considerable federal research funding focused on the supposed risk of MDMA induced neurotoxicity. Judge Pauley, in his 2011 opinion, accurately identifies that such concerns have often been exaggerated. While excessive use of what is often a poor quality product, taken with other drugs and alcohol and under adverse conditions by individuals with significant underlying vulnerability, may clearly lead to impaired neuropsychological and psychiatric status, it is equally apparent that modest dosages taken on only an occasional or single time basis, in the absence of other drugs or alcohol, and under optimal conditions by individuals with relatively good psychiatric and

medical health, do not appear to be associated with any clinically significant decrement of function. I have documented the serious methodological flaws along with misleading data interpretations present in some of the high profile MDMA neurotoxicity literature in several reviews I have published in psychiatric, neuroscience and drug abuse journals and textbooks over the last fifteen years. In recent years, however, there appears to be growing recognition that the fears of MDMA induced brain damage have been grossly overstated and consequently there has evolved considerably reduced media coverage of this issue.

- 20) Indeed, much of the preclinical laboratory evidence of neurotoxicity has been from small animal studies (usually with rats) where very high dosages of MDMA were injected into the animal, sometimes twice daily over multiple successive days, whereas recreational human users take MDMA orally and never inject the drug, virtually never take MDMA on successive days and almost always self-administer MDMA at least a week or often much longer apart and proportionally use far smaller dosages than the animals are injected with.
- 21) While recreational use has lessened over the past decade, interest has grown in MDMA's potential as an adjunct to psychiatric treatment, particularly in disorders that have proved to be refractory, or non-responsive, to conventional treatment. Formally approved studies have recently been conducted on patients with chronic, treatment-resistant post-traumatic stress disorder (PTSD). Published results indicate that while very good safety parameters were maintained during treatment, with no evident injury to subjects, treatment outcome was frequently excellent, with complete resolution of disabling symptoms in many of the individuals treated. Before its emergence as a popular recreational drug in the late 1980s and early 1990s, MDMA was considered to be a highly promising compound, when implemented in an optimally constructed treatment model, with potential application to a variety of difficult to treat psychiatric conditions. Regrettably, with the surging recreational use of "ecstasy", formal and approved clinical research with MDMA had to be put on hold. At the present time, however, with the growing appreciation of the genuine risk to benefit ratio of MDMA, it is now possible for properly accredited investigators to receive federal, state and local sanction to conduct research into MDMA's potential as a safe and efficacious treatment. As indicated above, my research group at Harbor-UCLA Medical Center and the Los Angeles BioMedical Research Institute is currently conducting an FDA approved investigation of the use of an MDMA treatment model with adults on the autism spectrum who have social anxiety.
- 22) Over the last twenty-five years I have published in the professional literature a number of research and review articles on MDMA. Some, though not all, of my publications are referenced in this document as follows:

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- 42) **Grob, C.S.** and Dobkin de Rios, M. Hallucinogens and related compounds: in R. Rosner (Ed.), Clinical Handbook of Adolescent Addiction. New York, Wiley-Blackwell, pp. 213- 223, 2013.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Executed on June 21, 2014 at Irvine, California.



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- Textbook, 4th Edition, Philadelphia: Williams and Wilkins, pp. 274-286, 2005.
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I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

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1980-1983 Psychiatry Residency, Cedars-Sinai Medical Center, Los Angeles, CA
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1984-1986 Medical Director, Psychiatric Services, John F. Kennedy Institute School, Baltimore, MD
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1987-1993 Director, Adolescent Psychiatry Unit, University of California Irvine Medical Center, Orange, CA.
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SPECIALTY BOARDS:

- 1984 Board Certified, American Board of Psychiatry and Neurology - Psychiatry
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PUBLICATIONS:

1. Grob, C.S.: Single Case Study: Female Exhibitionism,; Journal of Nervous and Mental Disease, 173:253-256, 1985.
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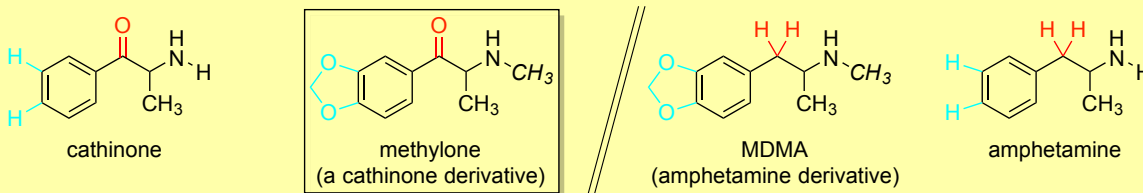
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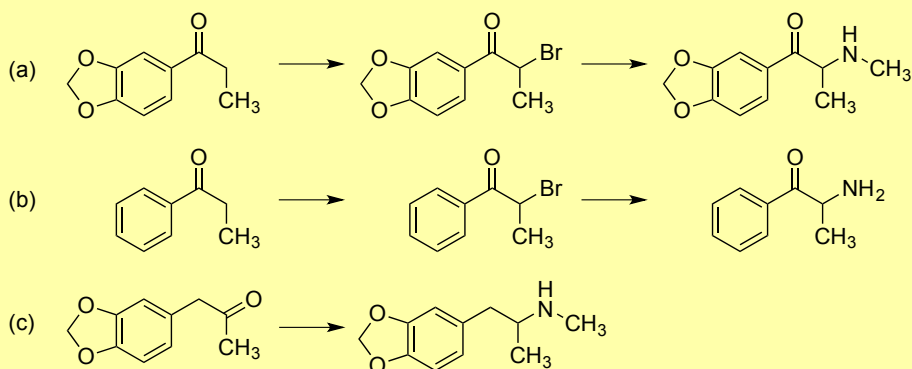
Appendix F

DECLARATION OF Dr. GREGORY B. DUDLEY, Ph.D.

1. I am over the age of 21.
2. I have personal knowledge of the matters contained within this Declaration.
3. I am an independent consultant specializing in organic chemistry and related fields.
4. I am an Associate Professor and Associate Chair in the Department of Chemistry and Biochemistry at Florida State University.
5. I received a B.A. degree in chemistry from Florida State University in 1995 and a PhD in organic chemistry from Massachusetts Institute of Technology in 2000. I was a postdoctoral research fellow in the Molecular Pharmacology and Chemistry program at the Memorial Sloan-Kettering Cancer Center in New York from 2000 until 2002.
6. I am an organic chemist with professional expertise in synthetic chemistry, chemical structure, molecular interactions, and structure-activity relationships. My primary research focus is on the synthesis of drugs and drug-like compounds. I have published and lectured extensively in these areas, as reflected in my CV, which is attached and referenced in full as Exhibit 1.
7. I have reviewed the chemical structures of methylone, cathinone, and methylenedioxymethamphetamine (MDMA) for the purpose of determining whether methylone is more similar to cathinone or to MDMA.
8. This Declaration is true and accurate to the best of my knowledge and information.
9. It is my expert scientific opinion that methylone more similar in chemical structure to cathinone than it is to MDMA.
10. Simple two-dimensional and color-coded representations of the chemical structures in question are provided in the graphic below.

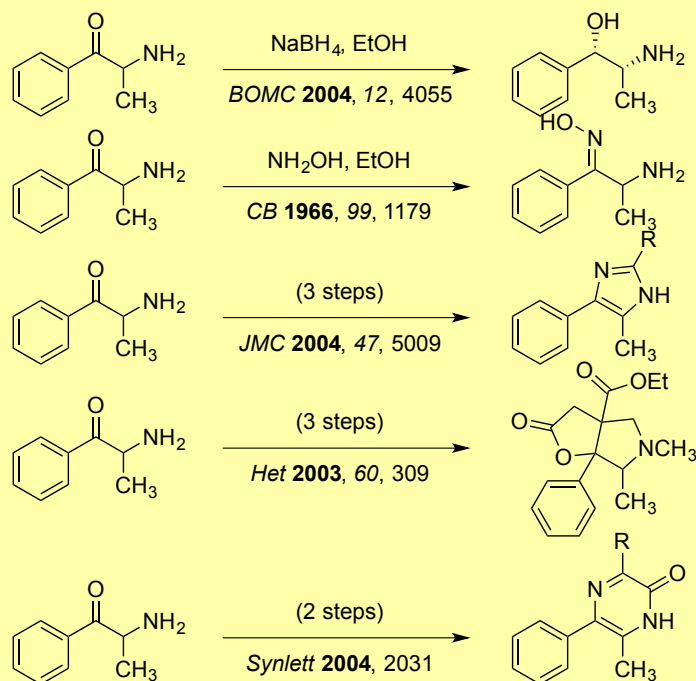


11. Structurally, methylone is classified as a “cathinone” to indicate that methylone includes the core structure of the substance found naturally in the khat plant, cathinone.
12. In contrast, methylenedioxyamphetamine (MDMA) is classified as an “amphetamine” because MDMA has the amphetamine core structure.
13. MDMA differs from amphetamine in the same way that methylone differs from cathinone: methyl group on nitrogen (in *italics*) and methylenedioxy fused to the aromatic ring (highlighted in light blue).
14. What distinguishes methylone from MDMA also distinguishes cathinone from amphetamine: the presence or absence of the ketone (highlighted in red).
15. Methylone is a cathinone, so the better comparison is to cathinone rather than the MDMA, which is an amphetamine.
16. Representative pathways for the chemical synthesis of (a) methylone, (b) cathinone, and (c) MDMA are provided in the graphic below.



17. Methylone can be formally described as a chemical derivative of cathinone.
18. Although methylone cannot easily be prepared directly from cathinone, synthesis of methylone and cathinone follow analogous routes (a and b).
19. The syntheses of cathinone and methylone follow similar paths, whereas the synthesis of MDMA is different.
20. The reason that the synthesis of MDMA is different is because *MDMA is an amphetamine, not a cathinone*.
21. Amphetamines like MDMA lack the ketone (**C=O**) functionality of the cathinones, so the synthesis is different.

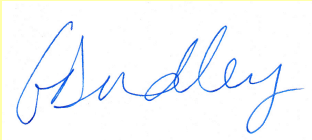
22. The ketone that differentiates cathinones from amphetamines is also responsible for many of the chemical properties of cathinones, as described below.
23. Examples of five chemical transformations of cathinone are presented in the graphic below.




24. In my expert opinion, each of these five transformations would be similarly applicable to methylone but not to MDMA.
25. I did not find any reactions that in my expert opinion would be applicable to MDMA and to methylone but not to cathinone.
26. The chemical reactivity of cathinones and amphetamines is different.
27. Cathinones and amphetamines both have amines (nitrogen groups), but only cathinones have the ketone ($\text{C}=\text{O}$) group, which opens up a much larger set of chemistries.
28. Therefore, I conclude that methylone is more similar in chemical structure to cathinone than it is to MDMA. Methylone is a cathinone. Its synthesis and reactivity patterns are those of cathinones, not amphetamines like MDMA.
29. My analysis and opinions regarding the chemical structures and chemical reactivities of methylone, cathinone, and MDMA would be accepted by the scientific community.

I declare under penalty of perjury under the laws of the State of Florida that the foregoing is true and correct.

Executed on June 20, 2014 at Tallahassee, Florida.

A handwritten signature in blue ink that reads "Dudley". The signature is written in a cursive style with a large initial "D".

GREGORY B. DUDLEY, Ph.D.

A solid black rectangular redaction box covering the text below the signature line.

Appendix G

DECLARATION OF ANTHONY P. DECAPRIO

I, Anthony P. DeCaprio, declare that the following is true and accurate to the best of my knowledge and if called as a witness I would testify to the following facts and opinions:

1. I am an Associate Professor of Chemistry and Biochemistry and serve as the Director of the Forensic and Analytical Toxicology Facility and the Forensic Science Certificate Program for the International Forensic Research Institute at Florida International University. I received a B.S. degree in biology from Rensselaer Polytechnic Institute in 1975 and a Ph.D. in toxicology from Albany Medical College in 1981. I worked as a research scientist in the area of human toxicology with the New York State Department of Health, Wadsworth Laboratories from 1981 to 1995. Since then, I have served in academic appointments at UAlbany and UMass Amherst prior to joining FIU in 2008.
2. I have 30+ years of professional scientific experience in the fields of chemistry and analysis of drugs, analytical/forensic toxicology, neurotoxicology and neuropharmacology of drugs and chemicals, and biomarkers of drug and chemical exposure. I have published over 75 original research papers in peer-reviewed journals, written several chapters for reference works in toxicology, and edited a book on biomarkers in toxicology. I provide expert peer-review services for numerous journals and funding agencies. I have delivered more than 80 research papers and invited lectures at universities, conferences, and private-sector companies. I am certified as a Diplomate of the American Board of Toxicology and am a full member of the American Chemical Society, International Society for Exposure Science, Society of Forensic Toxicologists, and Society of Toxicology. I regularly teach undergraduate and graduate courses in pharmacology and toxicology of drugs, analytical chemistry, and forensic toxicology. My qualifications and experience are detailed in my curriculum vitae, which is attached.
3. I have performed extensive research on novel psychoactive compounds (also known as “designer drugs”) of the stimulant and synthetic cannabinoid classes.

4. I have been asked to provide my opinions on the neurotoxicology and pharmacological potency of the drug known as “methyldone” in relation to MDMA (commonly known as “Ecstasy”).

Mode of Action of Central Nervous System Stimulants:

5. The mode of action (MOA) of most psychoactive central nervous system (CNS) stimulant drugs, including cocaine and certain drugs in the phenethylamine and cathinone class, involves modification of baseline levels of three major neurotransmitter molecules in the brain; dopamine, norepinephrine, and serotonin. Stimulant activity is generally due to increases in the levels of these neurotransmitters in the “synaptic cleft” present between two nerve cells (*i.e.*, the “presynaptic neuron” and the “post-synaptic neuron”). This is where neurotransmission takes place, by means of neurotransmitter molecules being released from the presynaptic neuron to bind with receptors on the post-synaptic neuron to stimulate (or, in some cases, block) a nerve impulse. While this is a highly simplified description of what is in reality a very complex process, the usual result of increased neurotransmitter levels in the synaptic cleft is an increased rate of firing of nerve impulses.
6. There are several cellular mechanisms that can underlie the increase in neurotransmitter levels induced by these drugs. Perhaps the most important involves a drug acting as a substrate and/or blocker of specific transporter proteins that are responsible for moving neurotransmitter molecules from the synaptic cleft back into the presynaptic nerve cell. Without this “reuptake” mechanism, neurotransmitters remain in the cleft and continue to excite the post-synaptic neuron. When operational, the reuptake system serves to limit and control the excitation rate of such neurons, which in turn modifies the activation state of the CNS as a whole.
7. For the three neurotransmitters most relevant to stimulant drugs of abuse, there is a specific transporter molecule present for each, *i.e.*, the dopamine (DAT), norepinephrine

(NET), and serotonin (SERT) transporters, respectively. A drug acting as a transporter “substrate” binds to the transporter and is brought into the nerve cell in preference to the normal neurotransmitter molecule. The effect of this process is to cause inhibition of reuptake and reverse transport of the neurotransmitter out of the cell and into the synaptic cleft. A drug acting as a transporter “blocker” binds to and blocks the movement of the transporter back into the cell, thus also blocking normal neurotransmitter reuptake. Methylenedioxymethamphetamine (MDMA) and cocaine are believed to be transporter substrates, while evidence indicates that cocaine is primarily a transporter blocker.

8. In addition to modifying reuptake of neurotransmitter molecules, certain stimulant drugs can directly induce release of neurotransmitter from the presynaptic nerve terminal. A third MOA involves those drugs that can “mimic” the normal neurotransmitter molecule and directly bind to and activate the specific neurotransmitter receptor on the post-synaptic neuron. In essence, these drugs compete with the normal neurotransmitter to activate the nerve cell.
9. The net result of all three of these possible mechanisms is the same, *i.e.*, elevated levels of neurotransmitters and increased stimulation of post-synaptic nerves.
10. Activation of dopamine, serotonin, and norepinephrine receptors results in different types of psychotropic effects. Dopamine mediates pleasure and reward pathways in the brain; repeated activation of dopaminergic neurons is strongly associated with addictive potential of a drug. High concentrations also induce restlessness and hyperactivity. Serotonin mediates a complex group of CNS responses, including mood, empathic feelings, and, at high concentrations, hallucinogenic activity. Norepinephrine mediates alertness, energy, and physiological parameters such as increased heart rate and blood pressure. The latter are commonly referred to as “sympathomimetic” effects.
11. Direct prediction of the relative pharmacologic activity of stimulant drugs is impossible based on 2D structure alone. Every phenethylamine and cathinone entity has a unique profile for modification of dopamine, norepinephrine, and serotonin activity. These will

in turn mediate the higher CNS effects of each particular drug. Because of the complexity of these interactions, pharmacological activity of a specific drug entity must be experimentally evaluated in *in vitro* (“test tube”) models, animal experiments, and, preferably, human studies to provide relevant data.

12. As discussed above, the psychotropic effects of stimulant drugs almost always involve binding with a transporter molecule and/or specific receptors for neurotransmitter molecules in the CNS. In order to assess the ability of prototypical drugs to produce these effects, initial studies often employ measurement of *in vitro* binding affinity with isolated receptors. The ability of a drug to bind to a specific receptor or transporter molecule can be measured by determining the K_i , the “equilibrium dissociation constant”. This parameter is defined as the concentration of the drug needed to occupy one-half (50%) of the specific binding sites at equilibrium. The smaller the value of K_i , the higher the affinity of the drug for the receptor. K_i values are often employed in drug development and other biomedical studies to provide some indication of how effectively a drug will (or will not) activate a particular receptor. This may (or may not) be correlated with a specific biologic, pharmacologic, or toxicologic effect.
13. In the case of phenethylamine and cathinone derivatives that cause neurotransmitter release or reuptake inhibition, one can also measure these phenomena in various *in vitro* model systems. The results of these tests are typically expressed as “ EC_{50} ” or “ IC_{50} ” values, which represent the concentration of drug needed to cause a 50% increase in the release rate or 50% decrease in the reuptake rate, respectively, of a particular neurotransmitter as compared to control. As with K_i measurements, the higher the activity of the drug in causing neurotransmitter release, the lower the EC_{50} or IC_{50} value.
14. Animal models have also been employed to help predict possible psychoactive effects of drugs in humans. Such models assess behavioral pharmacology endpoints such as locomotor activity, drug discrimination, and drug self-administration responses, in addition to physiological measurements such as body temperature and heart rate. While

offering additional data on the potential CNS activity of candidate drugs, these models all suffer from shortcomings when used to predict similar effects in humans, and therefore are best considered suggestive, but not selective, tools.

15. Pharmacological effects in humans are by their nature nuanced, graded, and variable. A “stimulatory” effect produced by two drugs that, on the surface, appears “similar”, may in fact be due to radically different pharmacological mechanisms. The phrases "pharmacological activity" and "pharmacological effect" are ambiguous and could refer to one of an almost unlimited variety of pharmacological properties. Examples of such properties include binding affinity of drugs to membrane and cytoplasmic receptors, enzymes, transporter molecules, DNA, RNA, or other molecular targets in addition to specific drug effects on liver, renal, CNS, lung, or any of a myriad of specialized cells. Such properties can also refer to functional effects on cognition, physiological parameters such as blood pressure and heart rate, sexual function, appetite, behavior, memory, locomotion, etc.
16. Because of the issues discussed above, the gold standard for assessing human CNS effects of potentially psychoactive drugs is monitoring such effects in humans themselves. This can include controlled experimental studies (*i.e.*, clinical trials) or well-documented case reports. For drugs of abuse, including synthetic cathinones and other derivatives, such data are not generally available. Consequently, prediction of comparative potency and efficacy of such drugs most often relies upon *in vitro* and animal data, a process that inevitably introduces uncertainty into these estimates.

Comparative Pharmacology of Methylone, Cathinone, and MDMA:

17. Methylone is a well-established member of the “novel psychoactive agent” class of drugs, having first been synthesized as a possible anti-Parkinsonism drug and first reportedly used as a recreational drug in 2004. Methylone was emergency scheduled as a Schedule I controlled substance (final order) on October 18, 2012. Methylone acts as

a mixed-action dopamine, serotonin, and norepinephrine transporter substrate, with differing potency for each (see below). Although a few animal studies have been conducted involving methylone and no human clinical trials have been published, a number of case reports have appeared in the literature outlining the CNS activity and toxicity of the compound.

18. MDMA was first synthesized in the early 1900s as a chemical precursor to other related drugs with possible uses to reduce bleeding. Following discovery of its psychoactive properties, the drug became widely used by medical professionals and for recreational purposes in the 1980s. MDMA was first made Schedule I in 1985. Considerable *in vitro*, animal, and human data are available for this drug.
19. A number of published, peer-reviewed *in vitro* and animal studies are available to assess the comparative pharmacological activity of MDMA and methylone. Details of these studies are discussed below.
20. Cozzi et al.¹ examined inhibition of monoamine neurotransmitter uptake by methylone and MDMA in several *in vitro* models. They reported that MDMA was approximately twice as potent as methylone in inhibiting reuptake of dopamine and serotonin and equipotent in inhibiting norepinephrine uptake. They also determined that MDMA was 13-fold more potent than methylone for inhibition of serotonin uptake by the vesicular monoamine transporter, VMAT2, which is a measure of the ability of the neuron to store the neurotransmitter for future release.
21. Nagai et al.² reported that MDMA was approximately 2- and 3-fold more potent than methylone in inhibiting dopamine and serotonin reuptake, respectively, into rat brain synaptosomes. They also determined that these drugs were roughly equipotent in norepinephrine reuptake inhibition. Similar relative potencies were noted for neurotransmitter release from synaptosomes.
22. Baumann et al.³ also using a rat brain synaptosome neurotransmitter release model,

showed that MDMA was approximately 3-, 2.5-, and 5-fold more potent than methylone for inhibition of norepinephrine, dopamine, and serotonin release, respectively. These researchers, using microdialysis techniques, also examined levels of dopamine and serotonin present in the nucleus accumbens (a brain region key to dopamine-based reward stimulation by drugs of abuse) following treatment with various stimulants, including MDMA and methylone. MDMA treatment at either 0.3 mg/kg or 1.0 mg/kg resulted in higher levels of both neurotransmitters in this brain region as compared to the same doses of methylone. Finally, repeated doses of 2.5 or 7.5 mg/kg of MDMA produced higher increases in body temperature in rats as compared to 3 and 10 mg/kg methylone, also consistent with higher potency of MDMA for this physiological endpoint.

23. In a later study, Baumann et al.⁴ assessed both neurotransmitter release and reuptake in rat synaptosomes following MDMA and methylone exposure. MDMA and methylone were approximately equipotent for inhibition of dopamine uptake, while MDMA was 3-fold more potent in stimulating dopamine release. For serotonin, MDMA was 8- and 6-fold more potent than methylone for inhibition of reuptake and stimulation of release, respectively. In addition, MDMA exhibited 3- to 4-fold higher potencies for both uptake and release of norepinephrine as compared to methylone.

24. In a very recent study, Eshleman et al.⁵ examined a number of neuropharmacological parameters, including transporter binding affinity, for MDMA, methylone, and other cathinones in a series of *in vitro* experiments. They reported that although methylone had a 4-fold higher affinity for the dopamine transporter than MDMA, this cathinone exhibited a lower potency (1.7-fold) for inhibition of dopamine reuptake than MDMA. These data show that transporter binding affinity does not always correlate with functional activity of a drug. In contrast, methylone exhibited both lower affinity (6-fold) for SERT and lower potency for serotonin reuptake inhibition (18-fold) than MDMA. Similar trends were observed for NET affinity and norepinephrine reuptake inhibition with the two drugs. In this study, MDMA was also found to be approximately 2- and 6-fold more potent than methylone for dopamine and serotonin release from

preloaded HEK cells, while both drugs had approximately equal potency for norepinephrine release. MDMA exhibited higher potency than methylone for a number of other relevant endpoints, including inhibition of serotonin uptake and norepinephrine release at VMAT2, in addition to higher affinity for the VMAT2 receptor. Finally, methylone was found to have 4- to 8-fold lower affinity for the three primary human serotonin receptors (*i.e.*, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}) than methylone.

25. Simmler et al.⁶ reported monoamine transporter binding affinity values for MDMA and methylone with trends similar to those found by Eshleman et al. Specifically, methylone affinity was higher for DAT, lower for SERT, and approximately equal for NET as compared to MDMA. However, in contrast to the great majority of other published work, these authors also reported a somewhat higher potency (3.5-fold) for dopamine reuptake inhibition by methylone as compared to MDMA. Comparisons for NET and SERT were similar to other reported data. Interestingly, in the same study, Simmler et al. also noted substantially lower potencies for stimulation of dopamine release (at least 5-fold) and serotonin release (at least 2-fold) from preloaded cells by methylone as compared to MDMA, in agreement with other published findings.
26. A few studies have also reported comparisons between MDMA and methylone in *in vivo* behavioral pharmacology and locomotor activity studies in animal models. Dal Cason et al.⁷ assessed stimulus generalization with methylone treatment in rats previously trained to discriminate MDMA from control. Methylone was able to substitute for MDMA in these experiments, but with lower potency and rate of response. Baumann et al.³ measured locomotor activity (a general measure of CNS stimulation) in rats following injection of the two drugs. MDMA was reported to be substantially more potent than methylone in increasing both horizontal locomotor activity and stereotypic movements. In contrast, López-Arnau et al.⁸ reported that MDMA and methylone were roughly equipotent in increasing locomotor activity in mice at a dose of 5 mg/kg. Miyazawa et al.⁹ compared the activity of 0.205 mmol/kg doses of methylone and MDMA for 10 functional and observational endpoints in mice. For 8 of the 10 measurements, MDMA was found to produce greater effects than the equal dose of methylone.

27. The bulk of pharmacological evidence presented above supports a conclusion that methylone is, on average, approximately 5-fold less potent than MDMA for a variety of endpoints relevant to the psychoactive effects of this class of drugs of abuse. Similar conclusions regarding a generally lower potency of the cathinone class of stimulant drugs as compared to MDMA have been published.^{10,11}

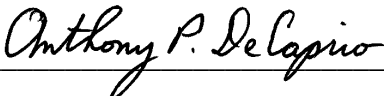
28. In their discussion of the background for methylone scheduling,¹² the DEA states *"Methylone also resembles MDMA in drug discrimination assays. Methylone fully substitutes (>80%) for MDMA in rats trained to discriminate MDMA from saline. Methylone (ED50=6.9 μmol/kg) was about half as potent as MDMA (ED50=3.5 μmol/kg) in these studies."* It must be noted that the DEA conclusion regarding relative potency of MDMA and methylone is based on a single unpublished contract study that is not available for independent evaluation, in contrast to the more comprehensive consideration of all published pharmacological data, including newer studies, presented above.

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DATED this 14th of July 2014.



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