UNITED STATES DISTRICT COURT
Northern District of New York
206 Federal Building
15 Henry Street
Binghamton, New York 13902

Thomas J. McAvoy
Senior District Judge

January 3, 2017

United States Sentencing Commission
One Columbus Circle, N.E.
Suite 2-500
Washington, DC 2002-8002

Attention: Public Affairs

To the Sentencing Commission:

I write in reference to your recent request for public comment on sentencing issues involving MDMA/Ecstasy, synthetic cannabinoids (such as JWH-018 and AM-2201), and synthetic cathinones (such as Methylone, MDPV, and Mephedrone). I currently preside over a case involving methylone distribution. The Defendant retained an expert who produced a report concerning the appropriate marijuana equivalency for methylone. The government responded to that report. After considering those documents, I obtained the report of an independent expert chemist. That expert addressed the questions of substantial similarity as required by USSG §2D1.1.

I would be happy to share those reports and the briefs and filings related to them with the Commission. Please contact my law clerk at the address below if you would like to have those documents forwarded to you.

Sincerely,

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May 24, 2016

via ELECTRONIC FILING
Senior Judge Thomas J. McAvoy
United States District Court
Northern District of New York
James T. Foley Courthouse
445 Broadway
Albany, New York 12207

Re: *United States v. Douglas Marshall, et al*
Docket: 14-CR-232

Your Honor:

As you are aware, this firm represents defendant Douglas Marshall in connection with the above-referenced case. We are writing to request a hearing in advance of sentencing, currently scheduled for June 13, 2016, to address a dispute concerning drug-equivalency under the Sentencing Guidelines.

As background, this case involves a conspiracy to sell a drug known as "methylone." Methylone is not a substance identified in the Sentencing Guidelines. *See* USSG § 2D1.1(c). Yet through a series of conversations with the defense, the government has made clear it intends to treat methylone as being five hundred times worse than marijuana—which is to say, it intends to pursue a 500:1 ratio with marijuana to determine Mr. Marshall's weight-based Guidelines enhancement.

District courts in this Circuit have repeatedly condemned this 500:1 ratio as inappropriate. Less than two years ago, for instance, the Eastern District of New York invited "[c]omprehensive expert testimony" on the issue, after which it held "[t]he 500:1 methylone-to-marijuana equivalency for sentencing guidelines ... relied upon by the government is rejected." *See, e.g., United States v. Chin Chong*, 2014 WL 4773978 (E.D.N.Y. 2014). Two years earlier

than that, the Southern District arrived at the same conclusion for MDMA—the same drug the government is analogizing to here—holding that "500:1 ... is greater than necessary to serve the objectives of sentencing." *United States v. Qayyem*, 2012 WL 92287, at *1 (S.D.N.Y. 2012). And it rendered the same holding the year before, as well, after hearing testimony from four expert witnesses. *See United States v. McCarthy*, 2011 WL 1991146 (S.D.N.Y. 2011).

Because the government wants this Court to split from *Chin Chong*, *Qayyem*, and *McCarthey*, the defense seeks a hearing to provide the Court with expert testimony further explaining why the proposed 500:1 ratio between methylone and marijuana is scientifically unsound. This proposed expert, in turn, is a professor in the Department of Chemistry and Biochemistry at Florida State University, has a Ph.D. in organic chemistry from MIT, and is a recipient of a National Institutes of Health Fellowship from Sloan-Kettering. With this in his background, Professor Gregory B. Dudley's enclosed report identifies exactly why "it would be hard scientifically to rationalize a marijuana equivalency for methylone more than 20% that of MDMA." And he is prepared to elucidate his reasoning in full view of the Court, subject to government cross-examination, provided that he be given the opportunity.

For these reasons, Mr. Marshall—as well as his co-defendant, Mr. Carlson—respectfully request a hearing in advance of sentencing to resolve the proper equivalency ratio between methylone and marijuana.

Thank you for your consideration.

Respectfully,

/s/ Bruce Barket
Bruce A. Barket, Esq.

cc: AUSA Wayne Myers (via ECF)

SENTENCING GUIDELINE CONSIDERATIONS FOR METHYLONE

Professor Gregory B. Dudley, Ph.D.
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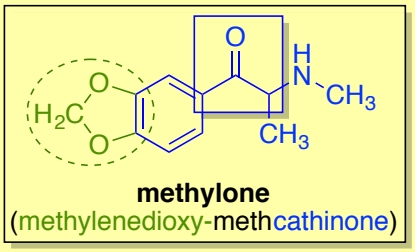
Tallahassee, FL 32306-4390, gdudley@chem.fsu.edu

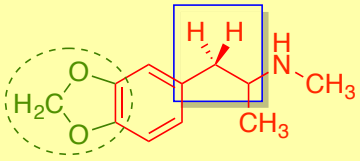
Overview

Methylone is not "*substantially similar*" (a legal comparative standard) in either chemical structure or pharmacological effects to any controlled substance listed in the Sentencing Guidelines. Therefore, it is not scientifically appropriate to treat methylone the same as any listed substance.

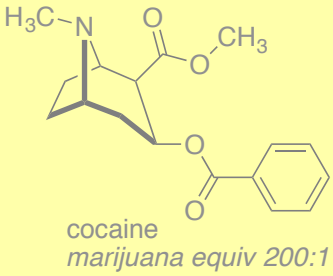
However, one can extrapolate from trends in how the Guidelines treat listed substances that are structurally and/or pharmacologically comparable to methylone to arrive at a reasonable marijuana equivalency treatment for methylone. For the reasons set forth herein, it would be hard scientifically to rationalize a marijuana equivalency for methylone more than 20% that of MDMA. Structures and marijuana equivalencies of some relevant substances along with methylone are illustrated below.



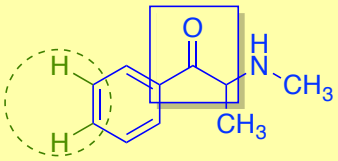
methylone
(methylenedioxy-methcathinone)



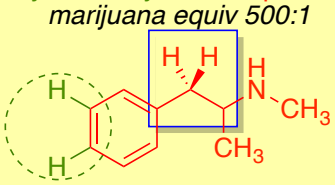
MDMA
(methylenedioxy-methamphetamine)
marijuana equiv 500:1



cocaine
marijuana equiv 200:1



methcathinone
marijuana equiv 380:1



methamphetamine
marijuana equiv 20,000:1

The rationale for this opinion is presented in three main parts, based on the three distinct considerations identified in the guidelines. These are (A) chemical structure, (B) pharmacological effects, and (C) potency. Definitions, criteria, considerations, and brief tutorials are included as appropriate.

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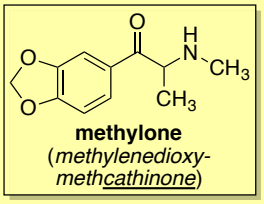
Executive Summary

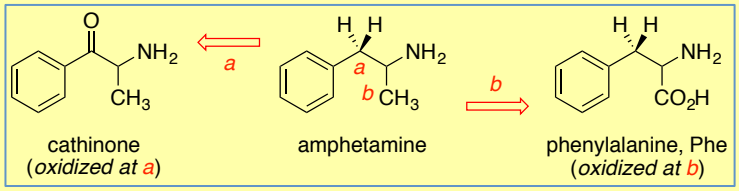


methylone
(*methylenedioxy-methcathinone*)

Methylone is not listed in the Sentencing Guidelines, nor is it "*substantially similar*" in chemical structure or in known effects on the central nervous system to any listed substance. "*Substantially similar*" is part of a legal comparative standard that, when met, allows different substances to be treated the same in certain contexts. It would not be appropriate to treat methylone the same as any listed substance.

However, methylone can reasonably be compared to—and contrasted with—a number of listed substances, including methcathinone, MDMA, and cocaine. The chemical structures of all of these substances are known and can be subjectively compared. The effects of methylone on the human central nervous system are not known, but available pharmacology data can be extrapolated hypothetically to make subjective comparisons of likely effects in humans "*to the extent practicable*". Pharmacology comparisons in this report focus on MDMA, because the government comparisons in this case focus on MDMA. Analogous comparisons to methcathinone would also be reasonable.

Part A. Chemical Structure. Methylone is the cathinone variant of the amphetamine MDMA. Cathinones and amphetamines are different classes of structures, and they are treated very differently in the Guidelines. For example, methcathinone is treated with *<2% the severity* of methamphetamine in terms of marijuana equivalency ratios. It would likewise be reasonable to treat methylenedioxy-methcathinone (methylone) much less severely than methylenedioxy-methamphetamine (MDMA).



cathinone (*oxidized at a*) amphetamine phenylalanine, Phe (*oxidized at b*)

Cathinones differ from amphetamines in the oxidation state of a specific carbon (carbon ***a*** in the adjacent graphic). Changes in oxidation state substantially impact the structure and function of molecular substances. For example, consider that the structural difference between amphetamine and cathinone is analogous to the structural difference between amphetamine and phenylalanine, an essential dietary nutrient. No one argues that phenylalanine (found in breast milk) is "*substantially similar*" to amphetamine. No one should hold the analogous opinions that cathinone is "*substantially similar*" to amphetamine, or methcathinone is "*substantially similar*" to methamphetamine. Likewise, methylone is not "*substantially similar*" to MDMA.

Part B. Effects. Methylone cannot be regarded as "substantially similar" to MDMA (or any other substance) in its effects on the central nervous system, because its effects are not well characterized. One can reasonably formulate the hypothesis that the human pharmacology of methylone is consistent with preliminary data from *in vitro* and *in vivo* (animal) studies and then compare preliminary data. Preliminary data can support various subjective conclusions, including that methylone is probably "MDMA-like", or "methcathinone-like", or even "cocaine-like". Different experiments highlight different aspects of methylone effects. Overall, it is reasonable to hypothesize that methylone has stimulant and entactogen properties.

Part C. Potency. As noted above, comparisons in this case focus on MDMA. MDMA is first and foremost an *entactogen*, with effects linked to perturbations in serotonin signaling pathways. *In vitro* data suggest that methylone may likewise perturb serotonin signaling pathways, but with potencies only on the order of 5-15% that of MDMA. In addition to its primary characterization as an entactogen, MDMA is a mild stimulant. Based on preliminary data and observations, methylone is probably also a stimulant. The relative potencies of methylone and MDMA may be more similar when analyzed for their secondary stimulant properties.

Concluding remarks. Methylone is a unique substance with its own unique suite of effects on the central nervous system. Given the requirement here to make comparisons to other (non-equivalent) substances listed in the Guidelines in terms of structure, effects, and potency, it is reasonable to extrapolate from MDMA when determining an appropriate sentence for methylone. *MDMA is an amphetamine and an entactogen. Methylone is a cathinone and probably a weaker entactogen. It would be hard to rationalize scientifically a marijuana equivalency for methylone more than 20% that of MDMA*.

Definitions and Considerations

Methylone is not listed in the Sentencing Guidelines. In such cases, the Guidelines offer instructions for how to proceed. *Paragraph 6 of Commentary following the Sentencing Commission guidelines on marijuana equivalency reads:*[1] *(emphasis added)*

> *"Analogues and Controlled Substances Not Referenced in this Guideline. — Any reference to a particular controlled substance in these guidelines includes all salts, **isomers**, all salts of isomers, and, except as otherwise provided, **any analogue** of that controlled substance. Any reference to cocaine includes ecgonine and coca leaves, except extracts of coca leaves from which cocaine and ecgonine have been removed. For purposes of this guideline **"analogue" has the meaning given the term "controlled substance analogue"** in 21 U.S.C. § 802(32). In determining the appropriate sentence, the court also may consider whether the same quantity of analogue produces a greater effect on the central nervous system than the controlled substance for which it is an analogue.*
>
> *In the case of a controlled substance that is not specifically referenced in this guideline, determine the base offense level using the marihuana equivalency of the most closely related controlled substance referenced in this guideline. In determining the most closely related controlled substance, the court shall, to the extent practicable, consider the following:*
>
> *(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.*
> *(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* **[i.e., potency]** *referenced in this guideline."*

A **"*controlled substance analogue*"** is defined in 21 U.S.C. § 802(32) to be a substance:

(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule I or II;

(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or

(iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II.

It is my understanding that these three Prongs are to be interpreted in the *conjunctive*: to satisfy the requirements, a substance must meet either (a) Prong One and Prong Two, or (b) Prong One and Prong Three.

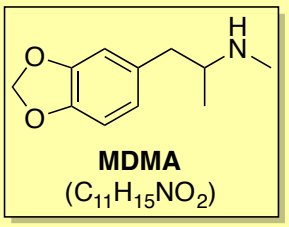
What is "*substantially similar*"? There is no scientifically accepted standard or definition of "*substantially similar*". Therefore, it can be difficult to interpret the definition of a Controlled Substance Analogue and Sentencing Guidelines scientifically; reasonable people might disagree on whether or not two substances are "*substantially similar*" in structure and/or central nervous system effects.

> If substances that are deemed to be "*substantially similar*" are treated the same in law, then "*substantially similar*" must mean *similar enough to be treated the same in law*.

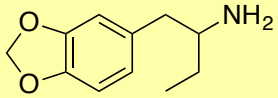
What is an *isomer*? Any reference in the Guidelines to a controlled substance includes all of its ***isomers***. However, the term "isomer" as applied is different from how it is used in chemistry. In chemistry, isomers are different structures having the same chemical formula (elemental composition). *The Guidelines reference to isomers* is restricted to optical isomers, positional isomers, and geometric isomers, and "positional isomer" is narrowly defined to emphasize the importance of functional groups in the structure (*from 21 CFR Part 1300.01, pages 8-9, with emphasis added):*

> *"As used in §1308.11(d) of this chapter, the term "positional isomer" means any substance possessing the same molecular formula and core structure and having the same functional group(s) and/or substituent(s) as those found in the respective Schedule I hallucinogen, attached at any position(s) on the core structure, but in such manner that no new chemical functionalities are created and no existing chemical functionalities are destroyed relative to the respective Schedule I hallucinogen. Rearrangements of alkyl moieties within or between functional group(s) or substituent(s), or divisions or combinations of alkyl moieties, that do not create new chemical functionalities or destroy existing chemical functionalities, are allowed i.e., result in compounds which are positional isomers. For purposes of this definition, the "core structure" is the parent molecule that is the common basis for the class; for example, tryptamine, phenethylamine, or ergoline. Examples of rearrangements resulting in creation and/or destruction of chemical functionalities (and therefore resulting in compounds which are not positional isomers) include, but are not limited to: Ethoxy to alpha-hydroxyethyl, hydroxy and methyl to methoxy, or the repositioning of a phenolic or alcoholic hydroxy group to create a hydroxyamine. Examples of rearrangements resulting in compounds which would be positional isomers include: Tert-butyl to sec-butyl, methoxy and ethyl to isopropoxy, N,N-diethyl to N-methyl-N-propyl, or alpha-methylamino to N-methylamino."*

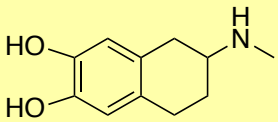
Three chemical isomers of $C_{11}H_{15}NO_2$ are illustrated below to exemplify the restrictions in place for which substances can be included among the controlled substances referenced in the Guidelines.



MDMA
($C_{11}H_{15}NO_2$)



isomer of MDMA
($C_{11}H_{15}NO_2$)
"positional isomer"



isomer of MDMA
($C_{11}H_{15}NO_2$)
NOT a "positional isomer"

Going from left to right, MDMA is a controlled substance listed in the Guidelines. The first isomer (middle) could be regarded as a positional isomer and be covered by Guideline references to MDMA. The second isomer of MDMA (right) would *not* be covered by Guideline references to MDMA. It is not a "positional isomer", although it is an isomer in chemistry.

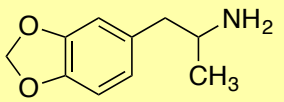
The definition of positional isomer reflects the importance of functional groups when considering chemical structures. One could argue that the first two structures are "substantially similar" (i.e., similar enough to be treated the same in law), but the third structure has different functional groups and thus different functions. It cannot be regarded as "substantially similar" in structure to the other two, despite having the exact same elemental composition.

The importance of functional groups in chemical structure transcends the definition of "positional isomer". Structures that have different functional groups have different functions and thus cannot be regarded as "substantially similar". This applies to isomers, and it applies to equally to non-isomers:

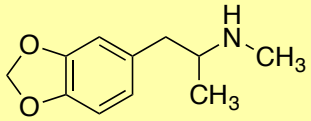
If structures that *are isomers* but do not share the same core structure and functional groups are not similar enough in chemical structure to be treated the same in law,
then compounds that *are not isomers* and do not share the same core structure and functional groups are also not similar enough in chemical structure to be treated the same in law.

What is an *analogue*? Any reference in the Guidelines to a controlled substance includes all of its ***analogues***. To a first approximation, substances that may be regarded as "substantially similar" in chemical structure and in central nervous system effects are treated the same in the Guidelines.

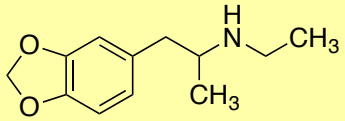
⟸ *(treated the same in the Sentencing Guidelines)* ⟹



methylenedioxy-amphetamine
(MDA)
marijuana equiv 500:1



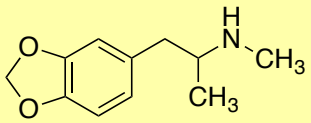
methylenedioxy-methamphetamine
(MDMA)
marijuana equiv 500:1



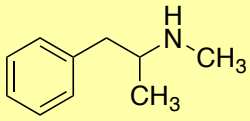
methylenedioxy-ethamphetamine
(MDEA)
marijuana equiv 500:1

For example, methylenedioxy-amphetamine (MDA), methylenedioxy-*meth*amphetamine (MDMA), and methylenedioxy-*eth*amphetamine (MDEA) are all Schedule 1 controlled substances and are listed in the Sentencing Guidelines as having identical marijuana equivalencies of 500:1. MDA, MDMA, and MDEA may reasonably be regarded as "substantially similar" substances.[2,3] Were they not already listed, it would be appropriate to treat MDMA and MDEA as analogues of MDA.

⟸ *(not treated the same in the Sentencing Guidelines)* ⟹



MDMA
marijuana equiv 500:1

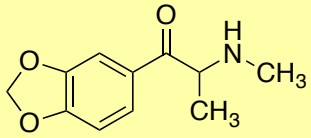


methamphetamine
marijuana equiv 20,000:1

methcathinone
marijuana equiv 380:1

On the other hand, MDMA, methamphetamine, and methcathinone are not treated the same in the Guidelines, and they may not be regarded as "substantially similar" in their chemical structures and in their effects on the central nervous system. In other words, it would be ***inappropriate*** to treat MDMA as an analogue of methamphetamine, or methamphetamine as an analogue of methcathinone, or vice versa, were they not all already listed. *If methamphetamine and methcathinone are not substantially similar in chemical structure, then MDMA and methylone are not either*.

Methylone is not an *isomer* or an *analogue* of any substance listed in the Sentencing Guidelines. In such cases, the Guidelines say to "*determine the base offense level using the marihuana equivalency of the most closely related controlled substance referenced in this guideline"* by considering — *"to the extent practicable*" — whether or not the unlisted substance is substantially similar to any listed substances in either chemical structure or effects on the central nervous system, and also how much of the unlisted substance "*is needed to produce a substantially similar effect on the central nervous system*".



methylenedioxy-**meth**cathinone
(MDMC, methylone)
marijuana equiv not det'd

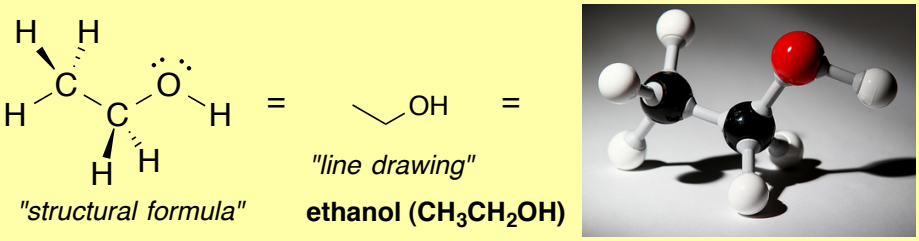
The Guidelines do *not* say to apply the marijuana equivalency of the most comparable substance to the unlisted substance (unless the unlisted substance is an isomer or analogue). It would not be logical to treat comparable substances as equivalent unless they are "substantially similar". As is noted in the *Background* section of the Guidelines, "*further refinement of drug amounts is essential to provide a logical sentencing structure for drug offenses*."

Part A. Chemical Structure

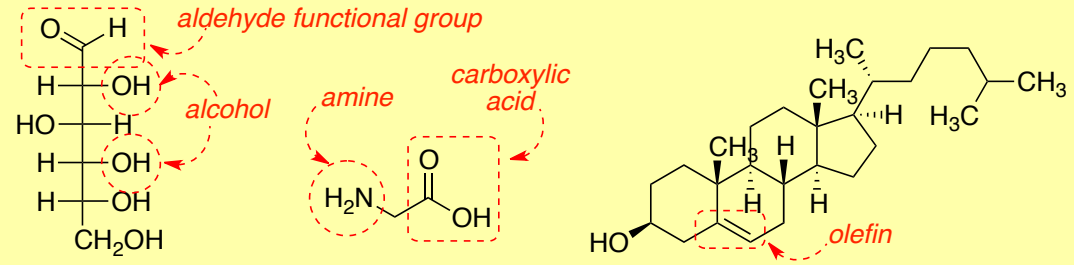
*"Whether the controlled substance not referenced in this guideline has a **chemical structure** that is substantially similar to a controlled substance referenced in this guideline."*

There is no substance listed in the Guidelines that is "*substantially similar*" in chemical structure to methylone. In my opinion, the two most comparable are methcathinone and then MDMA.

A brief tutorial on chemical structure. Organic compounds typically comprise a core ***framework*** of carbon and hydrogen atoms that define the size, shape, and dynamics (flexibility), and attached ***functional groups*** that impart specific chemical properties (patterns of reactivity and interaction with other molecules). Compounds are often illustrated graphically using line drawings, with lines to represent bonds (shared electrons) between atoms, and vertices to identify the location of atoms. Carbon and hydrogen atoms that are part of the core framework are often not labeled explicitly if they can be inferred from the line drawing.



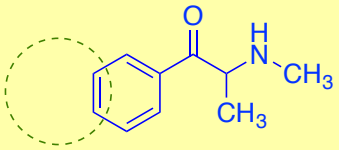
The chemical properties of the organic compound are based on the arrangement of functional groups in three-dimensional space, as well as the size, shape, and dynamics of the compound. Common functional groups include alcohols, olefins, amines, aldehydes, ketones, carboxylic acids, and halogens, with some examples provided in the compounds illustrated below. Some compounds, like sugars and amino acids, have a framework that is rich in functional groups. In compounds with fewer functional groups, like steroids, the shape of the carbon framework plays a larger role in determining its properties.



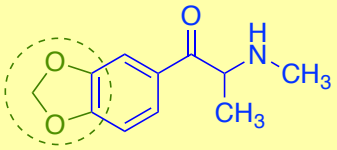
What is and is not "*substantially similar*"? As noted above, the term "*substantially similar*" is a legal term; it is not defined in the scientific literature. Indeed, *molecular similarity is impossible to define*.[4] Nonetheless, subjective similarity assessments are central to medicinal chemistry research. They provide a framework for generating new hypotheses, which then guide experimental designs. In the legal setting, molecular similarity assessments — centered around the standard of "substantially similar" — are used to guide policy.

In my opinion, *the carbon framework and functional groups are central to any assessment of molecular similarity*. (This opinion is consistent with the legal distinction between isomers in chemistry and "positional isomers", as discussed above.) Any change in functional groups is likely to have a significant impact on the overall chemical properties, and the more reactive the functional group, the more significant the change. A pair of structures having different cores and/or functional groups should not be regarded as "*substantially similar*", as discussed in the ensuing paragraphs.

Methylone is not "*substantially similar*" to methcathinone. Both methylone (methylenedioxy-*methcathinone*) and methcathinone share the "cathinone" core structure but differ in the presence or absence of the methylenedioxy ring fusion. Methylenedioxy — an example of an *acetal* functional group — contributes to the overall size, electronic structure, and reactivity profile of the molecule. However, acetals are generally less reactive than other functional groups. For example, ketones are often converted chemically into acetals in order to "protect" or mask the ketone functional group. This is done because acetals are generally less functional than ketones in chemical processes.

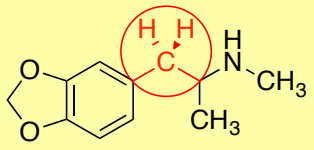


methcathinone
marijuana equiv 350:1

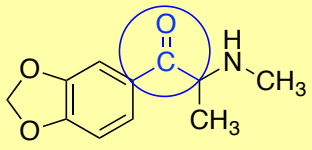


methylone
(methylenedioxy-methcathinone)

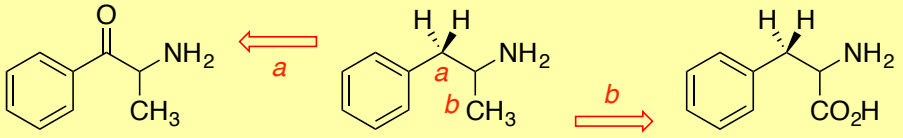
Methylone is NOT "substantially similar" to MDMA. Methylone is a cathinone, and MDMA is an amphetamine. The difference between a cathinone and an amphetamine is that *one carbon of cathinone is oxidized to its highest level relative to amphetamine*, resulting in the introduction of a ketone functional group. The importance of this structural change can be understood by considering a similar change to another familiar substance: ***phenylalanine*** (graphic below). Phenylalanine is one of the essential dietary amino acids. It is found in meats and even breast milk. The structural difference between phenylalanine and amphetamine is that *one carbon of phenylalanine is oxidized to its highest level relative to amphetamine*, resulting in the introduction of a carboxylic acid functional group. In my opinion, the structures of cathinone, amphetamine, and phenylalanine are comparable but not "substantially similar"; these substances and their respective chemical structures should not be treated interchangeably. Likewise, methylone is not "substantially similar" to MDMA.



MDMA
methylene group has the same bonding arrangement as in methane



methylone
ketone functional group has different bonding and chemical properties



cathinone
(*oxidized at a*)

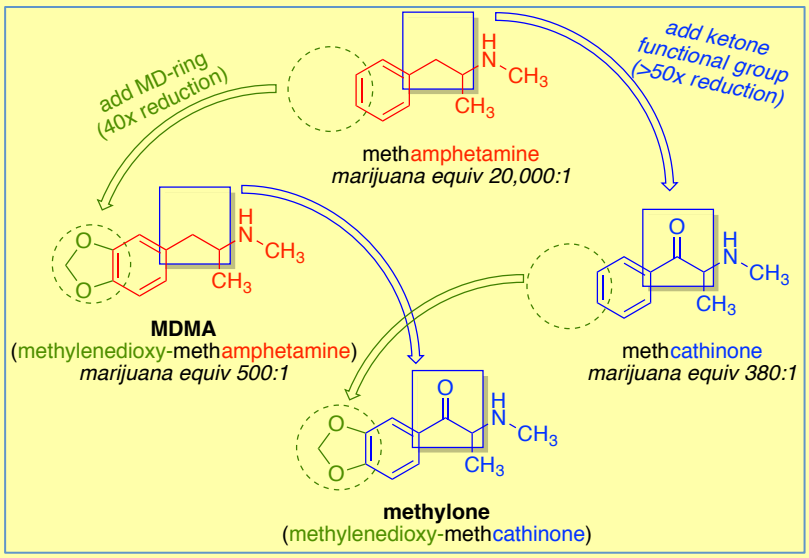
amphetamine

phenylalanine, Phe
(*oxidized at b*)

Guidance from the Guidelines. The Guidelines provide guidance on how to treat the ketone functional group and/or methylenedioxy ring system in methylone. Structures that differ from methylone in the absence of either and/or both of these features are listed in the Guidelines.

The structural difference between methylone (methylenedioxy-*methcathinone*) and *methcathinone* is the methylenedioxy ring. The methylenedioxy ring structure is also the structural distinction between MDMA (methylenedioxy-*methamphetamine*) and *methamphetamine*. Methamphetamine is punished 40x more severely than MDMA. If the cathinones were treated by logical analogy to the amphetamines, then the penalty for methylone would be substantially reduced relative to methcathinone, because the methylenedioxy ring is a mitigating structural feature.

The structural difference between methylone (methylenedioxy-*methcathinone*) and MDMA (methylenedioxy-*methamphetamine*) is the ketone functional group, which is also the structural distinction between *methcathinone* and *methamphetamine*. Methamphetamine is punished significantly — more than 50x — more severely than methcathinone. It would be logical based on chemical structure for the respective methylenedioxy-derivatives of methamphetamine and methcathinone to be scaled similarly. Therefore, based on structural considerations, the penalty for methylone should be substantially reduced relative to MDMA, because amphetamines are treated more severely than cathinones.



MDMA is not a cathinone. It does not have the ketone functional group. The ketone functional group is a significant difference between amphetamines and cathinones. Other structural features of MDMA are similar to methylone *but not identical*, because the impact of the ketone extends throughout the structure. The ketone fundamentally changes the structure and properties of the cathinones as compared to amphetamines.

Summary of Part A. The chemical structure of methylone is comparable to but not "substantially similar" to either methcathinone or MDMA. If one were to use comparable substances listed in the guidelines to determine a reasonable marijuana equivalency for methylone based on chemical structure, one would first take note of two trends. (1) Amphetamines are generally treated more harshly than cathinones; and (2) amphetamines without appended methylenedioxy ring systems are treated more harshly than amphetamines with methylenedioxy ring systems. The direct logical analogy to these trends would be to treat methylone (a methylenedioxy-cathinone) either (1) over 50x less harshly than the corresponding methylenedioxy-amphetamine, MDMA, or (2) 40x less harshly than the corresponding non-methylenedioxy-cathinone (i.e., methcathinone).

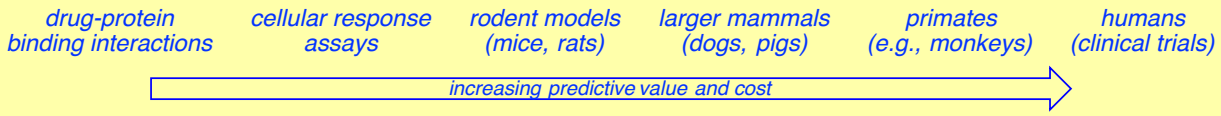
Part B: Effects on the Central Nervous System

"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."*

There is no substance listed in the Guidelines that can be stated with scientific certainty to be "*substantially similar*" to methylone in its effects on the central nervous system. The substances that are probably the easiest to compare to methylone based on the available data are MDMA and cocaine.[5]

A brief tutorial on pharmacology. Pharmacology is the study of drugs and their effects on living organisms. The effects that drugs have on the body stem from molecular interactions between the drug substance and biomolecules, typically proteins and protein complexes. These chemical interactions can be studied at the molecular, cellular, or whole-animal level to provide a detailed (albeit incomplete) understanding of drug action.

- **At the molecular level**, drugs can be quantified based on their ability to bind to specific proteins of interest. Of particular relevance to considerations are interactions involving a series of monoamine transporter proteins that regulate dopamine (i.e., the dopamine transporter protein, **DAT**), serotonin (i.e., **SERT**), and norepinephrine (i.e., **NET**).
- **At the cellular level**, drugs can be quantified based on cellular responses that arise, for example, from the drug interacting with the monoamine transporter proteins. Of particular relevance here are interactions that trigger the release and/or block the reuptake of monoamine neurotransmitters dopamine (DA), serotonin (5-HT), and norepinephrine (NE).
- **At the whole-animal level**, subjective responses of animals can be measured before and/or after administration of the drug. For example, animals change their activity levels in response to a stimulant, and caged animals choose to self-administer drugs that we regard as addictive. Finally, animals trained to perform a particular task in response to being given a particular drug may accept a similar drug as a cue to perform the same task.
    - There is a hierarchy of animal models that are increasingly reliable in terms of their relevance to humans but also increasingly expensive and complicated to perform. The easiest and cheapest but least predictive are studies done in rodents. New drugs will generally be tested first in rodents before moving up to higher mammals (e.g., dogs) and often to primates before testing in humans can begin.

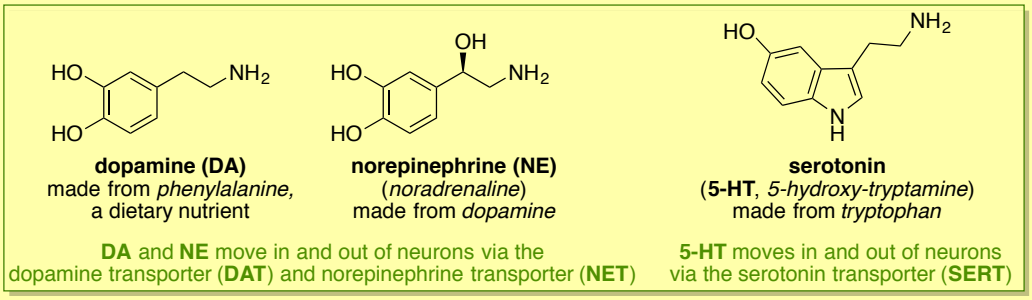


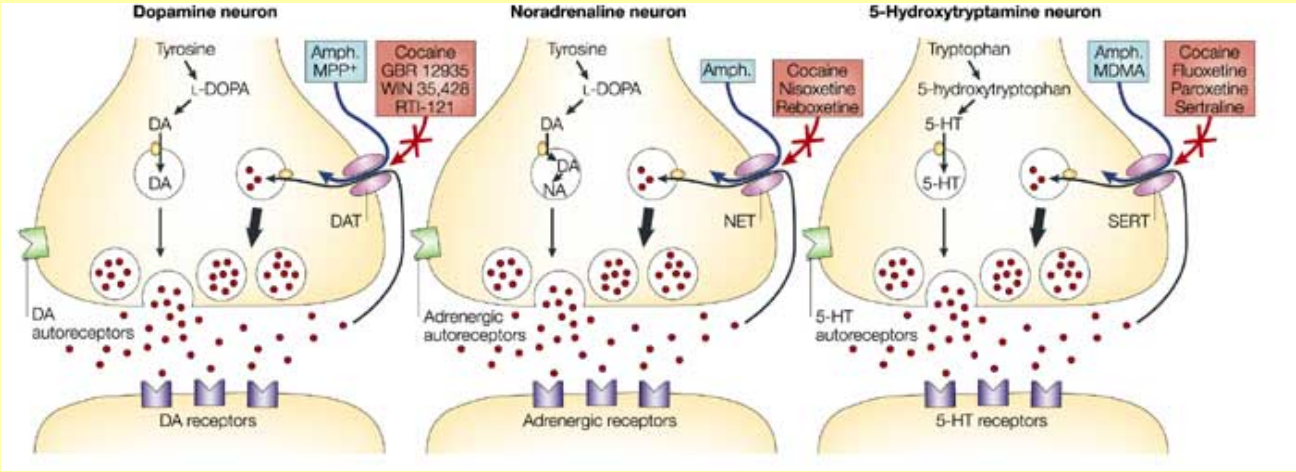
All of these types of pre-clinical studies provide important information that can be used to generate hypotheses as to how the drugs will perform in humans. Pharmaceutical researchers routinely use these studies to guide decisions on which drugs they will develop further toward the goal of putting a new pharmaceutical drug on the market. The same or similar tests are now being used by law enforcement to guide decisions related to the illegal designer drug market.

A major advantage of the aforementioned pharmacological studies is that they can (and therefore should) be performed in a controlled laboratory setting and compared against proper control experiments. Data that have been shown to be reproducible within a well-controlled study can be treated as reliable and compared quantitatively. When it comes to determining the pharmacological effects of new illegal designer drugs, a major limitation of these studies is that we typically cannot or should not (for ethical and/or cost reasons) conduct properly controlled pharmacological experiments in the higher mammals, primates, and/or humans. Thus, we can consider rigorous quantitative data from properly controlled studies, but we must recognize its predictive limitations. Additionally, one may

consider anecdotal evidence from reports linked to individual human users when formulating new hypotheses. Such anecdotal data, in my opinion, are best considered carefully as supplemental to scientific data. Anecdotal evidence from Internet forums, media clippings, emergency room and/or other medical reports, etc. can be compromised by placebo effects, exaggerations, misunderstandings, etc., as well as actual variations linked to individual users. A government expert is also on record downgrading such anecdotal data as compared to laboratory experimental data.[6]

Subjective classification of psychostimulant effects. Drugs like cocaine, methamphetamine, and MDMA can be referred to as psychostimulants. Psychostimulants act within our brain and central nervous system to change our neurochemistry, primarily by altering regulation of the neurotransmitters dopamine (DA), serotonin (5-HT), and norepinephrine (NE). To a first approximation, dopamine is related to our reward system and has been linked to addiction; serotonin alters our mood and has been linked to artificial feelings of euphoria; norepinephrine increases our ability to remain alert and stimulates activity and energy levels. These neurotransmitters relay messages through neural networks within and beyond the central nervous system. They are released by one neuron, recognized by the next to transmit the signal, and then taken back into the neuron through a transporter protein. Each neurotransmitter has its own transporter: namely, the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET). However, dopamine and norepinephrine are similar, and both DAT and NET can transport both DA and NE.[7]





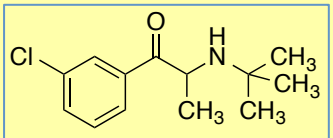
"FIGURE 1 | Schematic representation of dopamine, noradrenaline and 5-HT synaptic terminals. Monoamine transporters are localized to perisynaptic sites, where they are crucial for the termination of monoamine transmission and the maintenance of presynaptic monoamine storage. Several selective pharmacological agents acting at each monoamine transporter are shown. Amph., amphetamine; DA, dopamine; DAT, Dopamine transporter; L-DOPA, L-3,4-dihydroxyphenylalanine; 5-HT, 5-hydroxytryptamine; MPP^+, 1-methyl-4-phenylpyridinium; MDMA, (+)-3,4-methylenedioxymethamphetamine; NA, noradrenaline; NET, noradrenaline transporter; SERT, 5-HT transporter." ***(Figure reprinted from page 14 of reference 7)***

Psychostimulant effects of various amphetamines. Amphetamine and methamphetamine primarily act by stimulating the release of DA and/or NE from the neurons, thereby artificially elevating (i.e., perturbing) the extracellular levels of DA and/or NE in the synapse. This perturbation is associated with reward and heightened activity levels. *Methylenedioxy*-methamphetamine (MDMA), in contrast, acts primarily on serotonin levels, resulting in subjective feelings of empathy that have led to MDMA being characterized as an "*empathogen*" or "*entactogen*". Drugs that block the serotonin receptor attenuate the subjective effects of MDMA, lending credence to the prevailing view that subjective effects of MDMA are linked to perturbation of extracellular serotonin levels: MDMA enters the neuron via SERT and stimulates the release of serotonin into the synapse. Secondary to its effects as an entactogen, MDMA also has stimulant and hallucinogenic effects. The hallucinogenic effects of MDMA have been linked to MDMA associating directly with 5-HT receptors, thereby producing a false signal. In this regard, MDMA has been described as "LSD-like".

Psychostimulant effects of various cathinones. The pharmacology of cathinones is not as well characterized as that of the amphetamines. However, it is clear from extensive *in vitro* studies (using cells and/or biomolecules but not in live animals) and some *in vivo* studies (in animals) that many synthetic cathinones produce an array of effects linked to differential impacts on the regulation of dopamine, serotonin, and norepinephrine (cf. DAT/SERT ratio, below). Individual cathinone effects may be regarded as methamphetamine-like, MDMA-like, cocaine-like, etc., depending on whether the substance primarily interacts with DAT, SERT, or both (like cocaine), respectively.

(These classifications of subjective effects are made here based on how a substance interacts in a relative way with the different transport systems. How strongly the substances interact with each of the transport systems in an absolute sense (i.e., whether a greater or lesser quantity is needed to produce the relative effects) will be discussed in Part C on Potency.)

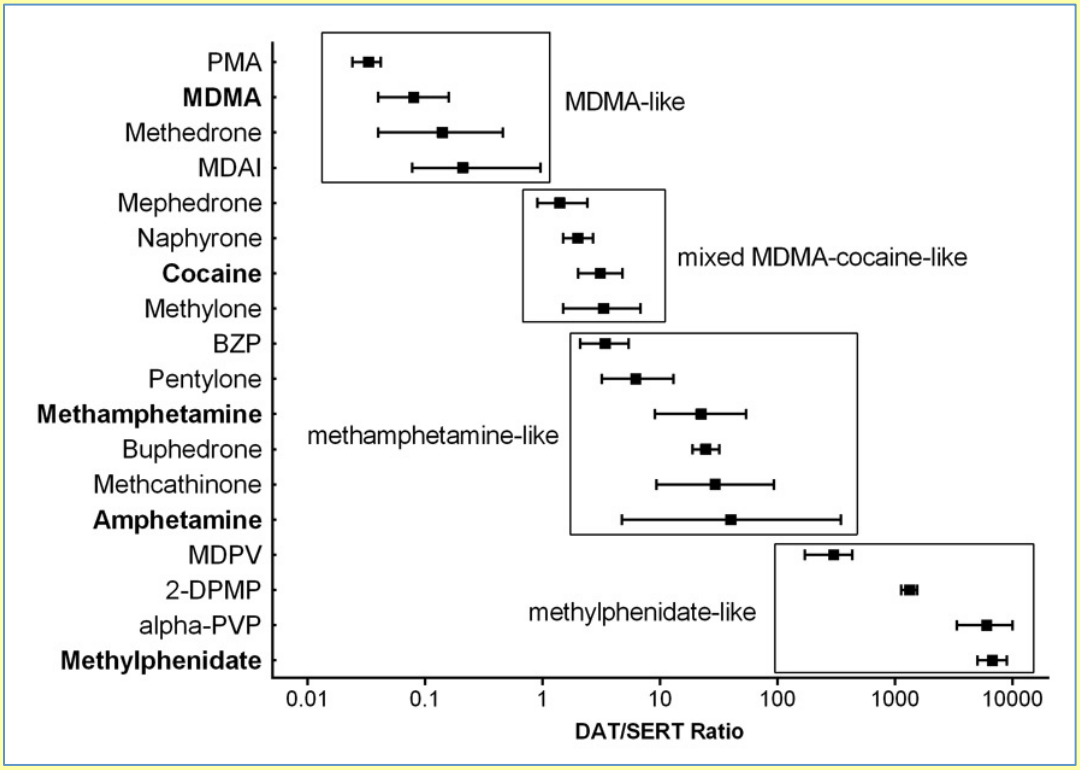
One well-studied synthetic cathinone is bupropion (Wellbutrin), which is prescribed for depression, smoking cessation, anxiety, and other indications related to neurochemical regulation. It primarily acts on serotonin transporters (SERT), with weaker impacts on DAT and NET in laboratory studies that do not seem to translate to human users.[8] (Buproprion can fully substitute for cocaine in drug discrimination studies,[9] as can nicotine;[10] *vide infra*.)



bupropion (Wellbutrin)
prescription cathinone

DAT/SERT ratio. The relative potency of a drug with respect to the dopamine (DAT) and serotonin (SERT) transporters is often used as a metric for estimating and comparing subjective effects. Drugs with similar DAT/SERT ratios might be subjectively classified together. Methylone has been described as "mixed-MDMA-cocaine-like" (see Figure on next page),[5] which reflects observations that methylone and cocaine have similar objective DAT/SERT ratios, but methylone had previously been regarded subjectively as "MDMA-like".[11,12] Our comparison focuses not on cocaine but on MDMA.[†] MDMA and methylone both act on DAT, SERT, and NET. However, the impact of MDMA is primarily linked to SERT, whereas methylone is regarded as non-selective or general with respect to the three transporters. Methamphetamine acts on DAT (and NET) but less on SERT. Thus, MDMA has a low DAT/SERT ratio, methamphetamine has a high DAT/SERT ratio, and methylone (along with several other cathinones and cocaine) has a mid-range DAT/SERT ratio of ~1–10.

[†] There is little structural similarity between methylone and cocaine, so the similar DAT/SERT ratios are likely a coincidental overlap of complementary biomolecular interactions. Subjective comparisons of methylone to MDMA and/or to methcathinone make more sense in the context of the current discussion than do comparisons to cocaine. Note that cocaine has a marijuana equivalency of 200:1.



"*Relative dopamine/serotonin inhibition potencies of selected novel psychoactive substances. Dopamine to serotonin transporter (DAT/SERT) inhibition ratios (mean ± 95% confidence intervals) for novel substances are shown in comparison with those of classic empathogens/entactogens (MDMA, ecstasy) and stimulants (cocaine, amphetamine, and methamphetamine). The ratios derived from in vitro studies help to predict the typically unknown clinical toxicity of novel substances. A low DAT/SERT inhibition ratio (<0.1) indicates tenfold greater relative serotonergic vs dopaminergic activity similar to MDMA. A high DAT/SERT inhibition ratio (>10) indicates greater relative dopaminergic vs serotonergic activity similar to methamphetamine. A high DAT/SERT inhibition ratio is a pharmacological characteristic associated with more stimulant effects and with higher potential for addiction." (Figure and caption reproduced from reference 5.)*

Drug Discrimination (DD) Studies One holistic gauge of subjective effects (and potency) is the drug discrimination study, in which trained subjects perform different tasks in response to different stimuli. Drug discrimination (DD) studies can be performed in human volunteers or in laboratory animals, and they can involve two or more stimuli. DD studies can provide important information regarding potential drugs of abuse, but they do not provide complete details. DD studies are "a perfect complement to other techniques".[13] A recent review of hallucinogen pharmacology provides a concise and clear description of DD studies (Nichols 2004, page 140, emphasis added):[14]

> "This technique is very powerful and produces robust effects at relatively low drug dosages that generally do not elicit other overt behaviors. In essence, the rat ''tells'' the experimenter, ''I think you gave me the training drug'' or ''I do not think you gave me anything.'' Although this type of yes/no result *obviously cannot provide information about the qualitative aspects of intoxication that the drug might produce in man*, at least it indicates whether the substance has overall pharmacological properties that resemble the training drug stimulus."

Two-choice drug discrimination studies can be used to identify commonalities in subjective effects, not that two substance are "substantially similar". The prescription cathinone bupropion (Wellbutrin, discussed above on page 11) fully substitutes for cocaine,[9] as does nicotine.[10] Bupropion, nicotine, and cocaine are all stimulants, but they do not have "substantially similar" effects on the central nervous system. Likewise, methylone[15] and methcathione[16] can fully substitute for both cocaine and

methamphetamine in rats, and they can both fully substitute for cocaine in monkeys.[17,‡] As noted below, methylone can also substitute for MDMA, but that does not mean that methylone has a "substantially similar" effect on the central nervous system as MDMA.

In 1997, Dal Cason and co-workers reported that methylone fully substitutes for MDMA in rats.[18] This early observation was probably influential in shaping the general perception that methylone is "MDMA-like". These data are consistent with methylone being capable of producing certain subjective effects that rats perceive to be "MDMA-like". Dal Cason and co-workers also asserted that MDMA can fully substitute for amphetamine, but other researchers "did not replicate these findings in rats",[19,20] which raises questions about the reproducibility of the Dal Cason DD study. Subjective "amphetamine-like" effects of MDMA run counter to profiles based on their quantitative DAT/SERT ratios[5] (cf. Figure above). It was later shown that rats can be trained to discriminate between the subjective effects of MDMA and amphetamine.[19]

What can we infer from DD studies? This collection of seemingly disparate data underscores the difference between saying that two drugs are comparable as opposed to "substantially similar". DD studies can tell you that two drugs might resemble each other in terms of particular effects, but they do not tell you that the effects of the two drugs are substantially similar. All of these drugs have stimulant properties (certainly more so than the saline reference); substitution in DD studies may simply reflect common stimulant properties of these different drug substances.

MDMA also has hallucinogenic properties; LSD can fully substitute for MDMA in rodents.[21] It can therefore be said that LSD is "MDMA-like", but not that LSD and MDMA are "substantially similar" in their effects on the central nervous system. For example, rodents can be trained to differentiate between LSD and MDMA, indicating that LSD and MDMA produce discernably different effects on the rodent central nervous system.

Summary of Part B. The effects on the central nervous of methylone are not known; no comparative pharmacology studies in humans could be found in the literature. Based on data from preliminary in vitro and in vivo studies, one can infer that methylone may be comparable—but not "substantially similar"—to either methcathinone or MDMA. The pharmacological effects of methylone have been characterized as "MDMA-like" or "mixed cocaine-MDMA-like". Analogous comparisons can be made between methylone and methcathinone. However, the pharmacological effects of methylone, MDMA, methcathinone, and/or cocaine cannot be described as "substantially similar" on the basis of objective and publically available pharmacological data.

When considering both structure and effects (Parts A and B), comparisons of methylone to MDMA and/or to methcathinone make more sense than to cocaine. The government in this case is making the comparison to MDMA. Discussion in Part C will focus on methylone vis-à-vis MDMA, but data for methcathinone and methamphetamine are also included.

‡ Methcathinone was 2x-3x more effective (lower dose, more potent) than methylone at producing subjective "cocaine-like" effects in these animal tests.

Part C. Potency ("*Whether a lesser or greater quantity…*")

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 **[i.e., potency]** *referenced in this guideline."*

Disclaimers and important considerations. There are several tiers of pharmacological data. The easiest tiers of data to acquire are generally the least predictive of human clinical outcomes, but the experiments best suited to gauging effects in humans would be impractical and/or unethical to perform. We must consider what data are available. I collected data from recent experiments in human cells, because these data provide the single most comprehensive picture from a relevant cellular model. *In vivo* and *in vitro* experiments in rodent models are also compared and discussed.

Further confounding the interpretation of pharmacological data is that reported values for a given pharmacological interaction can vary dramatically in the literature. Part of the problem stems from uncertainties and error rates, but a more confounding factor is that different labs have access to and/or employ different types of cells, proteins, animal models, and experimental protocols. Therefore, it is difficult (and often misleading) to compare results from different labs and different times. The best approach to comparing the potencies of two substances is to compare data from side-be-side experiments within the same study.

In gathering pharmacological data to report here for consideration with respect to methylone sentencing guidelines, I prioritized:

(a) recent data from primary peer-reviewed pharmacology journals
(b) comprehensive studies involving diverse and complementary experiments
(c) studies that directly compare methylone and MDMA in identical settings.

After carefully reviewing the literature (including searches in Google Scholar, PubMed, SciFinder, etc), I settled on two recent studies from highly regarded labs: Eshleman 2013[22] and Baumann 2012.[23] Eshleman's work is well cited and featured in several recent reviews,[5,11,12] and Baumann's lab at the National Institute on Drug Abuse was recently highlighted in a feature article in *Science* on designer drugs.[24] New data expand our understanding beyond previous reports; these recent studies have the advantage of presenting data for different substances from diverse experiments under internally consistent conditions. Therefore, one can compare data for the various substances with a higher degree of confidence. Eshleman's study includes the effects of methamphetamine, methcathinone, MDMA, and methylone on the release and the re-uptake of dopamine, serotonin, and norepinephrine in human cells. The Baumann study includes comparative effects of methylone and MDMA in rodents using both *in vitro* and *in vivo* experiments.

There is not enough data to make a firm conclusion regarding pharmacological effects and potency in humans. However, quantitative data from human cells and rodent models can and should be considered when forming the clearest picture possible. The advantage of these data is the rigor with which they were obtained. *The in vitro data and in vivo data presented and/or discussed here are reliable; Baumann and other studies have also shown good correlation between in vitro and in vivo cathinone pharmacology data*.[25]

Other pharmacological experiments can also provide quantitative data for comparing drug substances. Different experiments can provide different relative values, so it is critical to the present considerations that methylone and MDMA be compared directly using data taken from recent and comprehensive studies using a well defined and accepted experimental protocol. In terms of anec-

dotal information, there are reports of the estimated recreational doses for the certain substances. Although dosage *may correlate* broadly with potency, it also may correlate with the cost, availability, frequency of dosing, side effects and their severity, and other factors associated with the drug itself and/or the manufacturing and distribution processes. This report focuses on data from properly controlled scientific studies.

Potency data from drug discrimination (DD) studies Data from the 1997 Dal Cason study[18] described in Part B provide insights into potency as well as effects, but with caveats and concerns beyond those described in Part B. The authors state, in part: "*Because* [methylone] *(ED_{50} = 1.6 mg/kg; 6.9 μmol/kg) was about half as potent as MDMA itself (ED_{50} = 0.76 mg/kg; 3.5 μmol/kg), it would seem that here, too, the effect of carbonyl-oxygen introduction is to decrease potency*." However, they also write that: "*In terms of amphetamine-like activity,* [methylone] *(ED_{50} = 10.1 μmol/kg) is similar in potency to MDMA (ED_{50} = 7.5 μmol/kg)*" in rats, although as noted in Part B, other researchers failed to replicate this reported amphetamine-like activity for MDMA, and more sophisticated DD studies later differentiated between the activities of MDMA and amphetamine in rats.[19] The Dal Cason study is included in the present analysis, but it is not given more weight than recent and comprehensive studies, including ones (e.g. Goodwin 2000[19] and Baumann 2012[23]) that extend knowledge beyond where Dal Cason left off in 1997.

For example, even higher doses of methylone do not produce the same effect as MDMA. Dal Cason's experiment shows that a rat trained to recognize MDMA will identify methylone as being more like MDMA than like salt water, provided that effectively twice as much methylone is administered compared to MDMA. However, no quantitative information is provided on *how* the dose of methylone affects the rat's body temperature, neurochemistry, activity level, or other behavioral responses that potentially can be compared quantitatively for methylone and MDMA. Baumann's recent study[23] revealed important, quantifiable differences in how methylone and MDMA affect rodent behavior, physiological response, and recovery from large doses, as described on page 16.

Quantitative pharmacological data for methylone from experiments in human cells The Table on the next page outlines relevant data pertaining to the substances in question from Eshleman 2013,[22] including their respective abilities to stimulate the release and block the re-uptake of dopamine, serotonin, and norepinephrine through their actions on the various monoamine transporter proteins. In these experiments, a ***lower value reflects a stronger interaction***; the lower the number, the more potent the substance for a given interaction. The top portion of the Table presents the data as provided in the literature. The bottom portion re-presents reciprocal values for same data, normalized relative to methylone, which in my opinion makes interpretation somewhat easier. The columns are labeled using scientific terminology, with lay explanations provided the Table footnotes.

As can be seen in the Table, methylone is generally less potent than MDMA. For example, MDMA is 17x more potent than methylone in its ability to block re-uptake of serotonin, and MDMA is likewise more potent and effective at releasing serotonin. Improper regulation of serotonin levels is thought to be an underlying cause of euphoria ("ecstasy") or entactogenic effects experienced by MDMA users. These data suggest that methylone is probably substantially less effective than MDMA at producing a serotonin-mediated euphoric effect. Data from human cells can correlate with potency in human users, assuming that other important factors such as bioavailability are consistent for the two substances. Based on these data and the animal data described earlier and next, it is reasonable to conclude that MDMA is probably significantly more potent than methylone, especially when it comes to producing "MDMA-like" entactogenic and/or hallucinogenic effects.

Table 1. *Top Portion:* Raw pharmacology data from *in vitro* studies using human cells to measure the effects and potency of various drug substances on various human monoamine transporter proteins. *Bottom Portion:* A re-presentation of the same pharmacology data in a way that may be easier to interpret. Data are normalized to methylone (shaded in yellow). Red boxes indicate potency greater than that of methylone, and green boxes indicate reduced potency compared to methylone.

Potency and efficacy of various drug interactions with human monoamine transporters						
	re-uptake inhibition, IC_{50}, in μM[a]			monoamine release, EC_{50}, in μM (%max)[b]		
	hDAT	hSERT	hNET	hDAT	hSERT	hNET
methamphetamine	0.026	4.1	0.026	0.40 (102%)	22.5 (98%)	0.13 (93%)
methcathinone	0.14	13.5	0.031	3.6 (83%)	>100 (21%)	0.23 (149%)
MDMA	0.20	0.11	0.024	4.8 (104%)	1.04 (74%)	0.57 (116%)
methylone	0.34	1.9	0.23	11.8 (41%)	6.7 (78%)	0.43 (122%)
methamphetamine	13x	0.46x	8.8x	73x	0.37x	2.5x
methcathinone	2.4x	0.14x	7.4x	6.6x	<0.02x	2.3x
MDMA	1.7x	17x	9.6x	6.2x	6.1x	0.72x
methylone	***1x***	***1x***	***1x***	***1x***	***1x***	***1x***

[a] Reuptake inhibition keeps the neurotransmitter signal active. The IC_{50} values indicate how much of the drug is needed to reduce (by 50%) the ability of the transporter bring the neurotransmitter back into the cell.
[b] The monoamine release data determines how much of the drug is needed to release neurotransmitter from the cell (measured at its 50% threshold). The maximum amount of neurotransmitter that a drug is capable of releasing as compared to methamphetamine or other standard is given as the %max.

Comparison of *in vitro* and *in vivo* data on methylone and MDMA in rodent models At the National Institute on Drug Abuse (NIDA), Baumann et al[23] looked at the impact of methylone and MDMA using *in vitro* and *in vivo* rodent models. The *in vitro* work featured reconstituted rat brain synaptosomes, as they describe in their papers. Follow-up experiments on live rats resulted in "the first assessment of [methylone's] *in vivo* neurochemical actions." They found methylone *in vivo* to be "qualitatively analogous to" MDMA but "less potent, in agreement with *in vitro* results." However, Baumann noted "important differences" between methylone and MDMA. Most significantly, repeated exposure to MDMA caused *"persistent depletion" of serotonin in the rat's brains* (to as low as 24% of the normal levels), whereas *methylone caused "no long-term change" in monoamine neurotransmitter levels*.

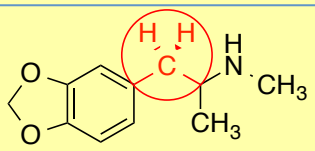
Summary of Part 3. Recent data from the Baumann lab at NIDA in rats demonstrate that: (a) there is good correlation between in vitro and in vivo experiments; (b) the immediate effects of methylone are qualitatively similar to but less potent than MDMA; and (c) repeated administration of methylone produced no evidence of long-term effects, whereas MDMA had a long-term negative impact on brain serotonin levels. Baumann's data from rat models are echoed in human cells by Eshleman's comprehensive evaluation of methylone and MDMA (among other psychoactive substances). Data from the Eshleman study were compiled, normalized to methylone, and tabulated above. Methylone and MDMA were both found to trigger release and block reuptake of dopamine, serotonin, and norepinephrine. In these six complementary experiments in human cells, the relative potencies for MDMA 0.72x, 1.7x, 6.1x, 6.2x, 9.6x, and 17x times the potencies for methylone.

Concluding Remarks

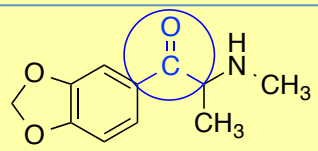
The illegal designer drug market has been described as an underground version of the pharmaceutical industry.[26] Whereas pharmaceutical companies aim to develop marketable therapeutics without infringing on competing patents, underground chemists aim to develop marketable drugs of abuse while staying ahead of the legal process. Regulatory controls over "positional isomers" and "analogues" of controlled substances have been powerful weapons against designer drugs, but they require a detailed understanding of medicinal chemistry to apply.

How to extrapolate from the Guidelines to reach a decision on methylone. MDMA and methylone are not "substantially similar" in structure or function, and they should not be equated under the law. However, a key phrase in the guideline instructions is open to multiple interpretations: "*determine the base offense level using the marihuana equivalency of the most closely related controlled substance referenced in this guideline…*" One interpretation is to identify the most closely related substance and use that value directly, as if the Guidelines said to "**[use]** *the marihuana equivalency*" directly as opposed to "*determine the…level using the marihuana equivalency"* as a guide. In my opinion, it is not appropriate to apply the same value for MDMA and for methylone. A more appropriate interpretation is thus one that recognizes the non-equivalency of comparable substances: to "*determine the base offense level using* [**as a guide**] *the marihuana equivalency of the most closely related controlled substance…*" The approach here is to extrapolate from MDMA when determining how to treat methylone in a manner consistent with the Guidelines.

The marijuana equivalency of MDMA is 500:1. What do we need to consider when extrapolating from this value to one appropriate for methylone?



methylenedioxy-**meth**amphetamine
(MDMA)
marijuana equiv 500:1



methylenedioxy-**meth**cathinone
(MDMC, methylone)
marijuana equiv not det'd

In terms of chemical structure, methylone differs from MDMA by its ketone functional group. The ketone functional group broadly differentiates cathinones from amphetamines, and marijuana equivalency tables treat the designer amphetamines much more severely than methcathinone or *khat*, the natural source of cathinone. For example, *methamphetamine is punished >50x more severely than methcathinone*. Other cathinone drugs like buproprion (Wellbutrin) are widely distributed by prescription without being subject to Schedule I or II controls. Based strictly on (A) chemical structure, the guidance from the Guidelines is that the penalty for the amphetamine MDMA should likewise be significantly (on the order of 50x) more severe than for the corresponding cathinone, methylone. In other words, *the penalty for methylone should substantially lower than for MDMA*.

In terms of pharmacological effects and potency, methylone is generally described in the literature as having either "MDMA-like" or "mixed MDMA-cocaine-like" subjective effects. Methylone is generally less potent than MDMA based on what quantitative pharmacological data are available. These substances act on different proteins in different ways to influence the levels of various neurotransmitters in the brain. Experiments focused on the various neurotransmitters provide distinct relative values for methylone and MDMA; in totality, it is not unreasonable to estimate that the potency of methylone is probably somewhere up to or around 20% that of MDMA.

If one were to focus on the serotonergic effects of methylone — i.e., the effects most similar to MDMA — then the estimated potency of methylone would be only 5–15% that of MDMA.

In conclusion, analyses of chemical structures and preliminary data on pharmacological effects and potency for the substances in question all indicate that the penalty for amphetamines should be greater than the penalty for cathinones, and that methylone is less potent than MDMA to the extent that they are similar. Therefore, the penalty for methylone (methylenedioxy-methcathinone) should be substantially lower than for MDMA (methylenedioxy-methamphetamine).

My Background and Expertise

I am a Professor and Associate Chair in the Department of Chemistry and Biochemistry at Florida State University (FSU) in Tallahassee, FL, and I hold an appointment on the Graduate Faculty in the College of Pharmacy and Pharmaceutical Science at Florida A&M University (FAMU) in Tallahassee, FL. I graduated *magna cum laude* with a B.A. in Chemistry from FSU in 1995, and I earned a Ph.D. in Organic Chemistry from the Massachusetts Institute of Technology (MIT) in 2000. I then received a National Institutes of Health (NIH) Fellowship to conduct postdoctoral research in Molecular Pharmacology and Chemistry at the Sloan–Kettering Institute for Cancer Research, the research wing of the Memorial Sloan–Kettering Cancer Hospital in New York, NY. I worked in this capacity from 2000–2002, at which point I joined the faculty of FSU as an Assistant Professor. I was promoted to Associate Professor with tenure in 2008 and Full Professor in 2015. I assumed Associate Chair responsibilities beginning in 2012.

My expertise is in synthetic, organic, and medicinal chemistry. My research interests focus on the development of new organic reactions and reaction technology, chemical synthesis of natural and drug-like compounds, and applications of synthetic organic chemistry in biomedical research. My research efforts have produced over 70 peer-reviewed publications, 7 invited contributions to leading reference works in organic chemistry, and multiple patents for innovations leading to two commercial products. I am called upon frequently to provide expert peer-review services for leading journals in chemistry (e.g., *Journal of the American Chemical Society*), organic chemistry (e.g., *The Journal of Organic Chemistry*), and medicinal chemistry (e.g., *ACS Medicinal Chemistry*) and major research funding agencies (e.g., National Institutes of Health, National Science Foundation, American Chemical Society). I have delivered well over 100 invited lectures at universities, scientific conferences, and pharmaceutical companies. I have received numerous awards and recognition related to research, teaching, and innovation, as outlined in the attached CV.

My consulting experience includes matters of chemistry and pharmacology for major pharmaceutical companies, small to mid-size biotechnology companies, entrepreneurial and economic development endeavors, and litigation support.

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June 2, 2016

VIA CM/ECF

Hon. Thomas J. McAvoy
Senior U.S. District Judge
Federal Building and United States Courthouse
15 Henry Street
Binghamton, New York 13901

Re: *United States v. Marshall, et al.*, 14-CR-232 (TJM)

Dear Judge McAvoy:

I write in response to the defendants' May 24, 2016 letter seeking a hearing to present expert testimony from a retained chemistry professor "to resolve the proper equivalency ratio between methylone and marijuana." Dkt. No. 53.

As an initial matter, the Probation Office disseminated the Presentence Investigation Reports over a year ago. *See* Dkt. Nos. 33, 34. Notably, neither defendant objected to the Probation Office's determination that the base offense level is 30, predicated on the proposition that MDMA, with a marijuana equivalency ratio of 500:1, is "the most closely related controlled substance" to methylone (i.e., "bk-MDMA"). U.S.S.G. § 2D1.1, Application Note 6 ("Application Note 6"). Indeed, in his May 26, 2015 objections to his Presentence Investigation Report, Mr. Carlson ***endorsed*** the marijuana equivalency ratio of 500:1, arguing that his total offense level was 25, after credit for timely acceptance of responsibility, if the Court were to agree with his position that a weapon enhancement under U.S.S.G. § 2D 1.1(b)(1) is inappropriate, thereby making him eligible for an additional two-level reduction under U.S.S.G. § 5C1.2. *See* May 26, 2015 Ltr. from A.Mysliwiec to M.Inman ("Given the above objections, I submit that Mr. Carlson's total offense level is 25."). From the inception of this prosecution over two years ago, the government has made it abundantly clear that it considers methylone most similar to MDMA under the Sentencing Guidelines, thereby triggering the marijuana equivalency ratio of 500:1 set forth in U.S.S.G. § 2D1.1, Application Note 8(D).

More fundamentally, the Probation Office properly calculated the defendant's marijuana equivalency pursuant to the directives of the Sentencing Guidelines and the United States Sentencing Commission ("Sentencing Commission"). Application Note 6 indicates that in cases involving controlled substances that are not specifically referenced in the Drug Table (such as

methylone), the Court must determine the base offense level using the marijuana equivalency of the most closely related controlled substance. *Accord United States v. Lababneh*, No. 15-2070-CR, 2016 WL 1612979, at *2 (2d Cir. Apr. 22, 2016) ("Where a controlled substance is not specifically referenced in the Guidelines, a court must calculate a defendant's base offense level by using the drug-equivalency ratio for the ***most closely related controlled substance*** found in the Guidelines.") (emphasis added). There is no authority in Application Note 6 which would allow the Court to alter the marijuana equivalency weights specifically listed in the Drug Table once the most analogous substance is determined.

Significantly, the professor's report does not identify a controlled substance listed in the Sentencing Guidelines that, based on the factors set forth in Application Note 6, is more "closely related" to methylone than MDMA. *See* Dkt. No. 53-1, at 9 (conceding "[t]he substances that are probably the easiest to compare to methylone based on the available data are MDMA and cocaine."). This is because there is no serious scientific dispute that, based on the three factors set forth in Application Note 6, of the controlled substances listed in the Sentencing Guidelines, methylone ("bk-MDMA") is "most closely related" to MDMA.[1] Fundamentally, the professor's report takes issue with the Sentencing Commission's ***policy decision*** to apply a marijuana equivalency ratio of 500:1 to unlisted substances (such as methylone) that are, based on the three factors set forth in Application Note 6, "most closely related" to MDMA.[2] Because the professor's report does not identify a substance that is more "closely related" to methylone than MDMA, using only the factors set forth in Application Note 6, his proffered testimony will not help the Court identity the correct base offense level under the Sentencing Guidelines.

At bottom, the professor's proffered testimony is a critique of the Sentencing Guidelines based on his opinion that "the penalty for methylone should [sic] substantially lower than for MDMA" and that "MDMA and methylone . . . should not be equated under the law." *Id.* at 17. Conclusions about the appropriate punishment for controlled substances are outside the bounds of a chemistry professor's expertise. Similarly, the professor's proffered testimony about how to interpret Application Note 6, *see id.* ("a more appropriate interpretation [of Application Note 6]

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[1] Ex. A, DEA, 3,4-Methylenedioxymethcathinone (Methylone) (2013).

[2] Application Note 6 provides:

> In determining the most closely related controlled substance, the court shall, to the extent practicable, consider the following:
>
> (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.
>
> (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.

is thus . . .") invades the role of the Court and is plainly improper. *See, e.g., Hygh v. Jacobs*, 961 F.2d 359, 363 (2d Cir. 1992) (district court must exclude expert testimony that "expresses a legal conclusion.").

To the extent that the defendants intend to seek a variance under 18 U.S.C. § 3553 predicated on the professor's opinions that methylone is less dangerous than MDMA, that the 500:1 marijuana equivalency ratio for MDMA is unsound policy, or that factors other than the three set forth in Application Note 6 (e.g., chemical reactions vs. chemical structure) it is well-settled that the Court may reject a policy judgment by the Sentencing Commission. *See generally Kimbrough v. United States*, 552 U.S. 85 (2007). The Court, however, is not obligated to reject a guideline range merely because it disagrees with a relevant policy judgment of the Sentencing Commission, nor is the Court required to "delve into the history of a guideline so that [it] can satisfy [it]self that the process that produced it was adequate to produce a good guideline. For if [it] is required to do that, sentencing hearings will become unmanageable, as the focus shifts from the defendant's conduct to the 'legislative' history of the guidelines." *United States v. Aguilar–Huerta*, 576 F.3d 365, 367–68 (7th Cir. 2009) (citations omitted). Additionally, "[t]he district court is not required, by either the Due Process Clause or the federal Sentencing Guidelines, to hold a full-blown evidentiary hearing in resolving sentencing disputes." *United States v. Slevin*, 106 F.3d 1086, 1091 (2d Cir. 1996); *see also United States v. Vassar*, 541 Fed. App'x 58, 60 (2d Cir. 2013) ("A criminal defendant ***has no right*** to demand an evidentiary hearing to present his own witnesses at sentencing . . . ." (quotation omitted and emphasis added). "All that is required is that the court afford the defendant some opportunity to rebut the Government's allegations." *Slevin*, 106 F.3d at 1086 (citations and internal quotations omitted). The Court may consider the defendants' criticisms of the Sentencing Guidelines as part of its overall assessment of a proper sentence under 18 U.S.C. § 3553.[3]

In a recent case affirming the 500:1 marijuana equivalency ratio for MDMA, the Sixth Circuit cautioned that, in light of Congress's direction to the Sentencing Commission to increase the penalties connected to MDMA crimes based on the perceived harmfulness of the drug, "a district court must find particularly persuasive policy reasons to reject the MDMA Guidelines range . . . ."). *United States v. Kamper*, 748 F.3d 728, 742 n.2 (6th Cir. 2014), *cert. denied*, 135 S. Ct. 882 (2014); *see also United States v. Bistline*, 665 F.3d 758, 764 (6th Cir. 2013) ("Thus, when a guideline comes bristling with Congress's own empirical and value judgments—or even just value judgments—the district court that seeks to disagree with the guideline on policy grounds faces a considerably more formidable task . . . ."). The Sentencing Commission is particularly well suited to consider the full scope of medical science and social norms on methylone and to receive all appropriate relevant information from the health, law enforcement, and educational communities concerning the impact and danger of methylone.

The majority of district courts apply the 500:1 marijuana equivalency ratio to methylone because methylone—as the defendants acknowledged in their written confessions to the DEA, "mimic[s] the effects of ecstasy (MDMA)," *see* Marshall PSIR, Dkt. No. 33, ¶ 13, and is "like

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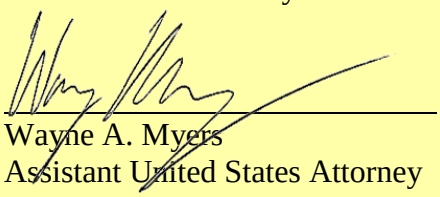
[3] Mr. Carlson, as part of his plea agreement, waived his right to appeal any sentence to a term of imprisonment of 188 months or less. Mr. Marshall, as part of his plea agreement, waived his right to appeal any sentence to a term of imprisonment of 121 months or less.

MDMA," *see* Carlson PSIR, Dkt. No. 34, ¶ 13—is sold, marketed, and consumed as a substitute for MDMA. *See, e.g., United States v. Borges, et al.*, 13-CR-2039 (S.D. Fla.), *United States v. Falsey, et al.*, 12-CR-029 (M.D. Fl.), *United States v. Guerrero*, 12-CR-390 (D.N.J.), *United States v. Martinez, et al.*, 13-CR-316 (E.D.N.Y), *United States v. Ordonez-Ramos, et al.*, 12-CR-20815 (S.D. Fl.). The Second Circuit has recognized that determinations by other federal courts may properly inform whether a referenced controlled substance is "most closely related" to one that is unreferenced. *See, e.g., United States v. Chowdhury*, 639 F.3d 583, 586 (2d Cir. 2011). The distribution of methylone is just as serious and dangerous as the distribution of MDMA and the punishments are, appropriately, commensurate. This Court is not obligated to recreate the wheel to arrive at the same conclusions reached by the United States Congress, the Sentencing Commission, and the majority of federal courts with respect to the dangerousness of MDMA and the appropriateness of treating methylone on par with MDMA.

If the Court is inclined to entertain additional submissions and/or conduct a hearing with respect to the propriety of the Sentencing Commission's 500:1 marijuana equivalency ratio for MDMA, or whether methylone is less dangerous than MDMA, the government intends to offer rebutting expert testimony from a DEA chemist and DEA pharmacologist addressing, *inter alia*, the chemical structure, pharmacological effects, potency, and dangerousness of methylone.

Very Truly Yours,

RICHARD S. HARTUNIAN
United States Attorney

By: 

Wayne A. Myers
Assistant United States Attorney

EXHIBIT A

Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section

3,4-Methylenedioxymethcathinone (Methylone)

["Bath salt," bk-MDMA, MDMC, MDMCAT, "Explosion," "Ease," "Molly"]

October 2013
DEA/OD/ODE

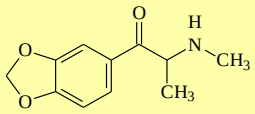
Introduction

3,4-Methylenedioxymethcathinone (methylone) is a designer drug of the phenethylamine class. Methylone is a synthetic cathinone with substantial chemical, structural, and pharmacological similarities to 3,4-methylenedioxymeth-amphetamine (MDMA, ecstasy). It is the β-keto analogue of MDMA. Animal studies indicate that methylone has MDMA-like and (+)-amphetamine-like behavioral effects. When combined with mephedrone, a controlled Schedule I substance, the combination is called "bubbles." Other names are given in the above title.

Licit Uses

Methylone is not approved for medical use in the United States.

Chemistry



Methylone
Molecular Formula $C_{11}H_{13}NO_3$

The core chemical structure of methylone identifies it as a phenethylamine, and it is related in chemical structure to MDMA differing only by an oxygen atom on the phenethylamine side chain. Methylone is a solid at room temperature. The Chemical Abstract Service (CAS) number is 186028-79-5 and the Chemical Abstract index name is 1-(1,3-benzodioxol-5-yl)-2-(methylamino)-1-propanone.

Pharmacology

There are substantial pharmacological similarities between methylone and MDMA. Methylone and MDMA, similar to cocaine and methamphetamine, inhibit in vitro the neuronal reuptake of the monoamines dopamine and serotonin and increase concentrations of these monoamines in the synaptic cleft. Similar to methamphetamine, methylone and MDMA also increase in vitro the neuronal release of these monoamines. An increase in monoamine concentrations in the central nervous system is thought to be involved in the pharmacological effects of these substances. 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. In rats trained to discriminate (+)-amphetamine from saline, both methylone (ED50=10.1 µmol/kg) and MDMA (ED50=7.5 µmol/kg) completely (>80%) substituted for amphetamine with similar potencies. Furthermore, methylone, similar to MDMA, does not substitute for 4-methyl-2,5-dimethoxyamphetamine (DOM), a Schedule I hallucinogen, in rats trained to discriminate DOM from saline.

Because of the structural and pharmacological similarities between methylone and MDMA, the psychoactive effects, adverse health risks, and signs of intoxication resulting from methylone abuse are likely to be similar to those of MDMA. Several chat rooms discussed pleasant and positive effects of methylone when used for recreational purpose.

User Population

Methylone, like other synthetic cathinones, is a recreational drug that emerged on the United States' illicit drug market in 2009. It is perceived as being a 'legal' alternative to drugs of abuse like MDMA, methamphetamine, and cocaine. Evidence indicates that youths and young adults are the primary users of synthetic cathinone substances which include methylone. However, older adults have also been identified as users of these substances.

Illicit Distribution

Law enforcement has encountered methylone in the United States as well as in several countries including the Netherlands, United Kingdom, Japan, and Sweden. The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state and local forensic laboratories in the United States. The System to Retrieve Information from Drug Evidence (STRIDE) provides information on drug seizures reported to and analyzed by DEA laboratories. Methylone was first identified by forensic laboratories in 2009, with four drug reports. In 2011, there were 1,857 methylone reports. The methylone reports more than doubled to 4,066 in 2012. From January to June 2013, laboratories have already identified 3,976 methylone reports. Methylone has been found in products falsely marketed as research chemicals, plant food, or bath salts. These products are often sold at smoke shops, head shops, convenience stores, adult book stores, and gas stations and can also be purchased on the Internet. Recently, methylone has been identified in law enforcement seizures that were initially suspected to be MDMA and marketed as "Molly".

Control Status

On October 21, 2011, methylone, it salts, isomers, and salts of isomers were temporarily controlled in Schedule I of the Controlled Substances Act (76 FR 65371). On April 12, 2013, the DEA published a Final Rule in the Federal Register permanently placing methylone in Schedule I.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section, Fax 202-353-1263, Telephone 202-307-7183, or E-mail ODE@usdoj.gov.

Rule 16 Summary of Expert Opinion and Bases

Report date: June 2, 2016

Prepared by: Thomas DiBerardino, Ph.D.

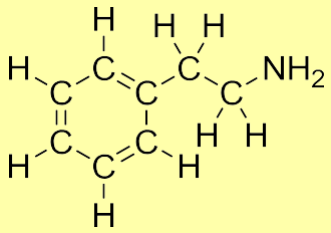
Substance at issue: 1-(1,3-benzodioxol-5-yl)-2-(methylamino) propan-1-one; 3,4-methylenedioxymethcathinone

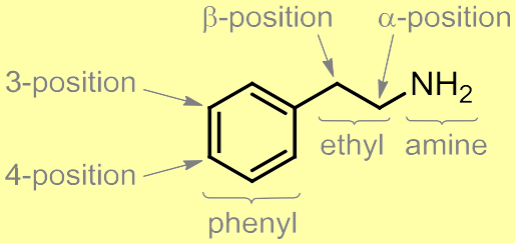
Alternate name: Methylone

Opinion: Under United States Sentencing Commission Guidelines Manual § 2D1.1, Application Note 6(A), methylone is substantially similar in chemical structure to 3,4-methylenedioxymethamphetamine (MDMA). This opinion is provided for purposes of sentencing under the federal sentencing guidelines only and is based on currently available information and literature.

Bases and Reasons:

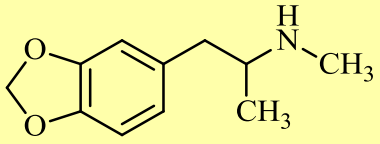
1. The core chemical structure of methylone and MDMA is phenethylamine. The figures below depict the chemical structure of phenethylamine. The figure on the left is a representation with every carbon (C) and hydrogen (H) atom shown for illustrative purposes. The figure on the right uses the most commonly used representation of chemical structures, with scientifically acceptable shorthand to depict carbon and hydrogen atoms. Labels indicate the positions of substitution and chemical groups discussed here.



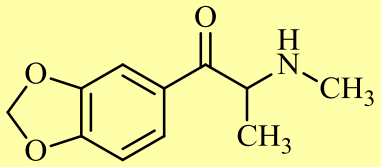


2. Methylone and MDMA share the same core chemical structure and are both substituted at the alpha (α)-position, on the phenyl ring, and on the nitrogen atom (N) of the phenethylamine core. Methylone is substituted with an oxygen atom (O) at the beta (β)-position, which is lacking in MDMA.

3. The chemical structure for each substance is shown below.



MDMA



Methylone

4. Both methylone and MDMA are substituted with the same alkyl group at the α-position of the phenethylamine core. This alkyl group is a methyl group (-CH_3).
5. Both methylone and MDMA are substituted with the same alkyl group at the nitrogen atom of the phenethylamine core. This alkyl group is a methyl group.
6. Both methylone and MDMA are substituted with the same methylenedioxy (-O-CH_2-O-) group at the 3,4-positions of the phenyl ring.
7. Methylone and MDMA share the same core chemical structure and are both substituted at the α-position, on the nitrogen (N) atom, and on the phenyl ring with the same groups.
8. In comparing the chemical structures for methylone and MDMA, as depicted in #3 above, the difference in the chemical structures is minor and consists of only the addition of an oxygen atom at the β-position of methylone. Therefore, methylone is substantially similar in chemical structure to MDMA.
9. MDMA is the substance listed in the guideline that has a chemical structure most closely related to the chemical structure of methylone.

Rule 16 Summary of Expert Opinion and Bases

Report date: June 8, 2016

Prepared by: Li Fang, Ph.D.

Substance at issue: 3,4-methylenedioxy-*N*-methylcathinone

Alternate name(s): methylone, β-keto-MDMA, MDMC

Opinion: Under United States Sentencing Commission Guidelines Manual § 2D1.1, Application Note 6 (B), methylone has a stimulant effect on the central nervous system that is substantially similar to the stimulant effect on the central nervous system of 3,4-methylenedioxy-N-methylamphetamine (MDMA), a Controlled Substances Act (CSA) Schedule I substance. This opinion is provided for purposes of sentencing under the federal sentencing guidelines only and is based on currently available scientific data and literature.

No substances beyond those identified in the Drug Equivalency Tables as described have been considered for purposes of this report.

Bases and Reasons:

USSG 2D1.1 Application Note 6: (B)

1. *In vitro* functional assays are used to evaluate the activity of a drug or substance. In laboratory studies investigating the effects of drugs on monoaminergic systems, methylone, like MDMA, has been shown to bind to dopamine, serotonin, or norepinephrine transporters and to inhibit the uptake of the corresponding monoamine neurotransmitters in transfected cells *in vitro*.
2. Central nervous system (CNS) stimulants produce a range of behavioral responses such as an increase in locomotor activity. Data from locomotor activity experiments (*in vivo* studies) demonstrate that methylone, like MDMA, increases locomotor activity in rodents.
3. The drug discrimination study (*in vivo* study) in animals is one of the most selective animal models used to predict stimulant-like subjective effects in humans. In the drug discrimination paradigm, if a new drug or substance has discriminative stimulus effects in animals similar to a known drug of abuse, this new drug or substance highly likely to produce pharmacological and subjective effects in humans similar to the known drug of

abuse and would be similarly abused by humans.

a. In rats trained to discriminate MDMA from saline, methylone fully substitutes for the discriminative stimulus effects produced by MDMA.
b. In rats trained to discriminate (+)-amphetamine from saline, both methylone and MDMA fully substitutes for amphetamine.

4. Currently, like MDMA, there is no accepted medical use of methylone in the U.S.

USSG 2D1.1 Application Note 6: (C)

1. A good correlation exists with respect to drugs of abuse between discriminative stimulus effects in animals and the reported subjective effects in humans.
2. In the drug discrimination study, a greater quantity of methylone is needed to produce a substantially similar effect on the central nervous system as MDMA.
    a. Data from drug discrimination studies demonstrate that methylone (ED_{50}=6.9 μmol/kg) fully substitutes for the discriminative stimulus effects produced by MDMA (ED_{50}=3.5 μmol/kg) in rats.

Li Fang, Ph.D.
Drug Science Specialist
Drug Enforcement Administration

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Li Fang, Ph.D.
Drug Science Specialist
Drug Enforcement Administration

ANALYSIS OF METHYLONE CHEMICAL STRUCTURE, EFFECTS, AND POTENCY RELATIVE TO DRUGS IN THE SENTENCING GUIDELINES

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Chemistry of Life Processes Institute, Northwestern University
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Introduction and summary of findings

The drug methylone is not listed in the Sentencing Guidelines, and thus lacks a settled marijuana equivalency, a common problem for emerging "designer drugs" that have not been extensively studied and are developed to skirt existing drug laws[1-3]. In the case of *United States v. Douglas Marshall, et al,* the government suggests that methylone is substantially similar to MDMA and should be used as the basis for sentencing, indicating a marijuana equivalency of 500:1 for methylone. In response to this claim, the defense submitted an expert report by Professor Gregory Dudley from Florida State University, who is an expert in Synthetic Organic Chemistry. Dr. Dudley's academic work is related to, and likely overlaps with, the fields of Medicinal Chemistry and Bioorganic Chemistry, making him a well-qualified choice to serve as an expert in this trial. Dr. Dudley concludes that methylone lacks substantial chemical or pharmacological similarity to MDMA, and that its potency is roughly 20% that of MDMA.

I have been asked by Sr. Judge Thomas McAvoy to prepare an independent report analyzing the similarity of methylone to MDMA and other drugs in the Sentencing Guidelines. I find that methylone's chemical structure is substantially similar to that of MDMA and that Dr. Dudley's arguments to the contrary go against a broad scientific consensus which views methylone as an MDMA analog first and foremost[2, 4-7]. I find that the available pharmacological data about methylone's subjective effects (i.e. as a stimulant or hallucinogen or entactogen) suggest in very broad terms that it is similar to MDMA, cocaine, and methamphetamine[8], however that its effects in humans have never been scientifically studied and cannot be confidently inferred from the available data. Finally, I conclude that the data about methylone's potency as compared to that of MDMA is indeterminate. Some studies suggest decreased entactogenic potency, while others suggest increased stimulant potency[2, 8]. Dr. Dudley's report focused on studies that suggested reduced potency of methylone relative to MDMA[9, 10], yet other reports are available which suggest comparable or increased potency of methylone relative to MDMA[8, 10-12]. Ultimately, the available *in vitro* and animal studies data is totally inadequate to infer the potency of methylone in humans with any degree of reasonable confidence as is highlighted with related examples at the end of the report[10, 13-15].

A. Methylone Chemical Structure

To answer: "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."

Summary

Methylone is the beta-keto analogue of MDMA. The chemical structure of methylone is substantially similar to MDMA based on basic chemical principles and consensus of the scientific community.

Isomerism

The expert report by Dr. Dudley correctly details why methylone is not an isomer of MDMA or any other drug in the Guidelines in either the legal or chemical sense.

Methylone is a keto or methylenedioxy analogue of MDMA or methcathinone, respectively

Methylone can be chemically compared to many amphetamine-related drugs listed in the Guidelines, some of which are shown in **Figure 1** with their marijuana equivalencies. Methylone is the beta-keto analogue of MDMA, meaning MDMA can be converted to methylone through addition of a single oxygen atom at the appropriate site, along with removal of two hydrogen atoms. Methylone is also technically the methylenedioxy analogue of methcathinone, meaning that methcathinone can be converted to methylone through addition of one carbon and two oxygens, connected as a methylenedioxy ring fusion (see **Figure 1**) at the appropriate site.

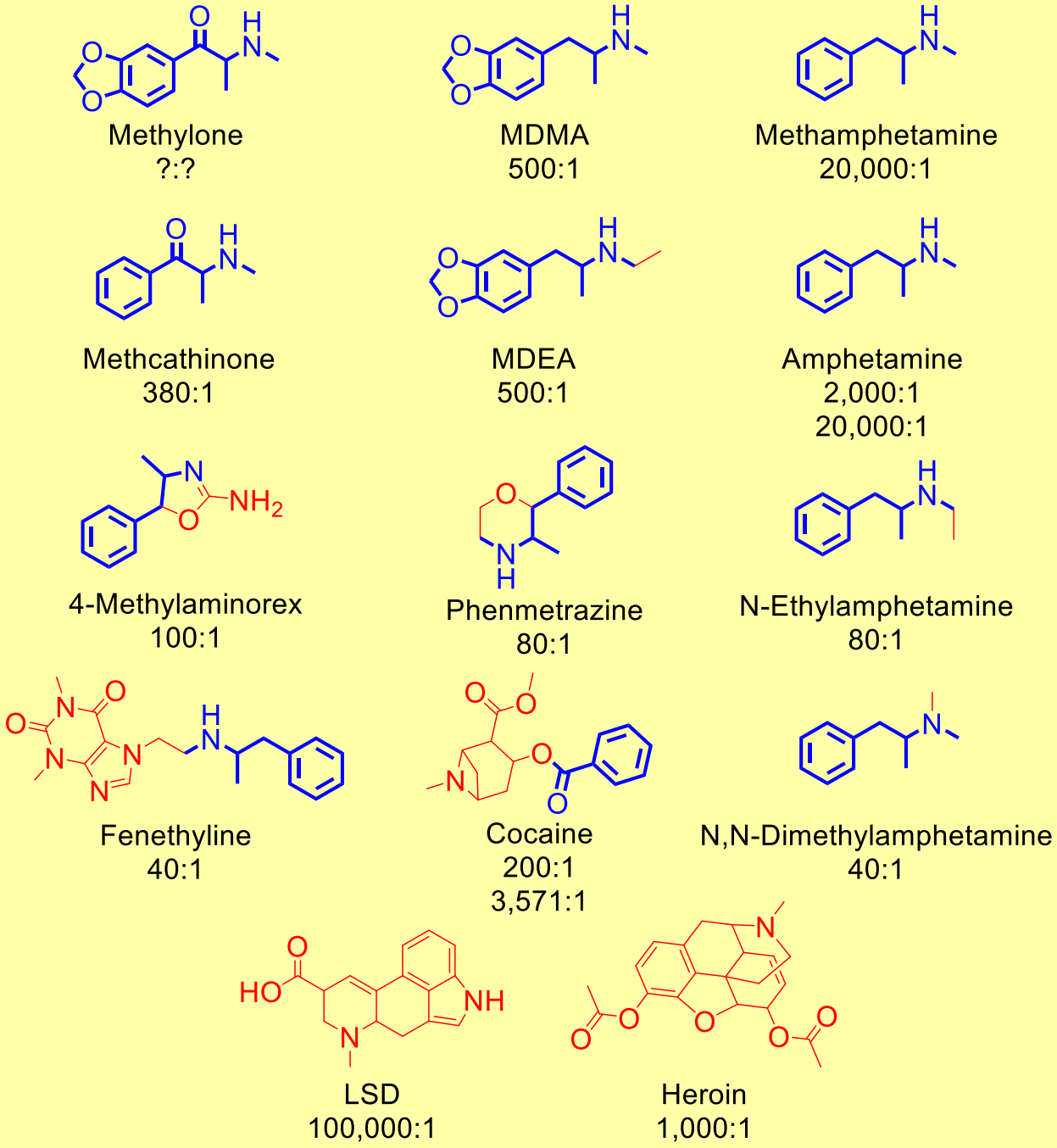

Figure 1: Chemical structures of methylone and related drugs from the Sentencing Guidelines. Structural features of each drug that are shared with methylone are shown in blue with thicker lines. Structural features that are not shared with methylone are shown in red with thinner lines. The drugs LSD and heroin are shown as examples of chemically unrelated drugs.

Methylone is chemically similar to MDMA

The methylenedioxy functional group (or acetal) of methylone likely causes a larger change to methylone's chemical structure than its ketone group since it adds more atoms and

creates a second ring structure. Thus, in my opinion, the chemical structure of methylone is more similar to MDMA than it is to methcathinone which lacks the methylenedioxy functional group. While different chemists could view this question differently, I believe most would agree that MDMA and methylone are very closely related, since the ketone substitution is simple and has a limited, mostly local effect on the overall molecule's shape and polarity. Furthermore, of all the structures shown in **Figure 1** (or present in the Guidelines), only MDEA is as chemically similar to MDMA as methylone is. MDEA and methylone are similar in that they both differ from MDMA by only one functional group addition. Notably, MDEA and MDMA also share the same marijuana equivalency. *Given all the above information, I believe it is reasonable to consider the chemical structure of methylone "substantially similar" to the structure of MDMA.*

Consideration of the defense report on chemical similarity

Strict meanings of chemical isomerism, salts, and chemical structure are accurately presented by Dr. Dudley. However, in my opinion, his analysis of what constitutes legal chemical analogues (i.e. non-isomeric, but substantially similar molecules) is fundamentally flawed and unparsimonious. In short, Dr. Dudley claims that the definition of substantial similarity is to be inferred from the relationship between drugs with different marijuana equivalencies in the Guidelines. Though tempting on the surface, this logic is obviously false, since drugs that are dissimilar both in chemical structure and pharmacology can have identical marijuana equivalencies, such as is the case for the three drugs Codeine, Phenmetrazine, and Diethyltryptamine (**Figure 1**). Each of these come from a different class of drugs and have different pharmacological activities and chemical structures, yet share a marijuana equivalency of 80:1. Similar marijuana equivalencies in the Guidelines cannot be used as precedent for a broad definition of substantial chemical similarity, or to infer the specific effects of functional groups.

Furthermore, Dr. Dudley suggests that the addition of functional groups to methamphetamine-type structures reduces their marijuana equivalency. This is also false. For example, the addition of a methylene functional group to MDMA to create MDEA does not affect its marijuana equivalency. Thus, the claim that the addition of a ketone to MDMA (creating methylone) should necessarily reduce its marijuana equivalency is untenable. Dr. Dudley claims that oxidation in particular has a special power of reducing potency (such as addition of a ketone to MDMA to form methylone). However, he does not offer any evidence for this claim. In reality, the effect of a single functional group substitution cannot be predicted on the basis of chemical theory, and must be empirically determined[16]. Moreover there is no reason to think a ketone would either increase or decrease the potency of MDMA. Some substitutions will increase potency, others will reduce potency, and others still will have little or no effect.

Conclusion

Substantial similarity should be based on the scientific community's consensus on the structure of methylone. *The scientific community widely treats methylone as an MDMA analogue first and foremost[2, 4-7].* Methylone contains the entire structure of MDMA, except that it adds the ketone functional group, which has only a limited effect on the overall shape of the molecule. The structure of methylone is plainly inspired by MDMA and methylone was originally synthesized with the intention of imitating MDMA[17]. MDMA is the most similar guidelines drug to methylone (**Figure 1**). Moreover, methylone is more similar to MDMA than any other Guidelines drug is similar to MDMA, other than MDEA, which has an identical marijuana

equivalency to MDMA (**Figure 1**). *Thus in my opinion, methylone's chemical structure is similar to MDMA in a specific manner. This makes methylone and MDMA substantially similar.*

B. Methylone Subjective Pharmacology

To answer: "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 the guidelines."

Summary

There are no rigorous scientific studies of the effects of methylone in humans, and the available studies cannot determine the hallucinogenic, stimulant, or depressant effects of methylone in humans. Anecdotal reports from human users suggest the subjective effects of methylone are similar to those of MDMA[17, 18]. Available *in vitro* and animal data suggests methylone may have similar effects as MDMA and cocaine on the levels of certain neurotransmitters in the human brain[19]. This may mean that the subjective effects of methylone in humans are similar to MDMA, as well as cocaine. The scientific literature generally views methylone as most pharmacologically similar to MDMA[8, 11, 20]. In my opinion, the available evidence about methylone's subjective effects neither confirms nor refutes its substantial similarity to MDMA or other stimulant drugs in the Guidelines. Further research may reveal that methylone is pharmacologically substantially similar to drugs in the Guidelines such as MDMA, methamphetamine, and either powder cocaine or cocaine base[11].

Pharmacology and types of pharmacological data

In lay terms, pharmacology is the study of how individual molecules or mixtures of molecules influence biological systems such as cells, tissues, organs, or whole organisms. What is most relevant to *United States vs. Douglas Marshall, et al*, is how methylone affects subjective human experience by acting as a stimulant, a hallucinogen, a depressant, or an entactogen. The latter (entactogen) effect is not listed explicitly in the Guidelines, however represents a key component of the well documented subjective effects of MDMA. Another word for entactogen is "empathogen". Both words refer to an intense feeling of love of self and of people in the drug user's physical vicinity while high on the drug.

United States vs. Douglas Marshall, et al is concerned specifically with the subjective effects of methylone in whole humans. Unfortunately, the available pharmacological data does not address methylone subjective effects in humans. Instead, the available data either reports the molecular action of methylone *in vitro* using rat or human cells (i.e. its ability to perturb synaptic levels of specific neurotransmitters) or else attempts to measure the subjective effects of methylone in rats, i.e. its effect as a stimulant. There can be, and often are, very large discrepancies between a drug's effects *in vitro* or in animals, relative to its effects in humans[13] and this concern will be discussed at greater length at the end of **Part C**.

Studies of methylone's molecular effects in human cells and studies of its subjective effects in rats are of equal value and importance in my opinion. The molecular system in *in vitro* human cells is the exact same molecular system found in whole humans, which strengthens *in vitro* studies in human cells. However, the *in vitro* system is uncoupled from broader physiology and subjective experience, which are key to the case at hand. There are differences between

the molecular system in rats and in humans, as well as between rat and human physiology and subjective experience, which weakens studies in rats. However, studies in rats enable speculation on how methylone might affect other whole organisms, such as humans or other higher mammals (i.e. dogs, monkeys, apes, etc.), such as is needed for this case. Overall, both types of data should be considered. However their direct relevance to the subjective effects of methylone should be viewed with a high degree of skepticism. This will be discussed further in **Part C**.

Pharmacology of methamphetamine related drugs

Page 10, section "Subjective classification of psychostimulant effects" of the report prepared by Dr. Dudley adequately describes the general pharmacology of methamphetamine and cocaine related drugs (like MDMA and methylone) as it pertains to this case. To paraphrase, it is believed that in general these drugs function by increasing levels of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) in synaptic junctions in the brain. DA is related to addictiveness, 5-HT can cause euphoria, and NE relates to alertness. Different stimulant drugs like MDMA and cocaine increase the levels of these neurotransmitters in human brain synapses in different combinations. Importantly, the levels of specific neurotransmitters **cannot** be conclusively linked to drugs' subjective effects in humans. It is possible that other molecular mechanisms are important, or that the levels of these neurotransmitters are affected in unexpected ways. For example, it is not fully understood what the source of the intense "entactogenic" effects of MDMA are, yet these effects are vital to the subjective experience of MDMA[2].

Pharmacological effects and classification of methylone

Pharmacological research of methylone has been conducted outside of humans, with the hope of gaining insights into how it possibly might function in humans. These studies have used cultured human cells *in vitro*, rat synaptosomes *in vitro*, and living rats, among others[8-12].

Studies in living rats have focused on the effects of methylone on animal behavior, including the ability of methylone to substitute for other drugs such as cocaine, MDMA, and methamphetamine, and the ability of methylone to alter coordination and activity[4, 20]. Collectively, these studies suggest that methylone is likely to function as a stimulant. MDMA, cocaine, and methamphetamine are all considered stimulants, so these studies suggest that methylone is broadly related to all these drugs.

In vitro studies have typically focused on directly measuring the biochemical effect of methylone, i.e. its ability to alter the levels and distribution of the neurotransmitters DA, 5-HT, and NE in brain tissue, including human brain tissue. Levels of these neurotransmitters are expected to be related to methylone's subjective effects in humans, though it is not possible to determine a drug's effects in humans on the basis of *in vitro* data or neurotransmitter levels. These studies have revealed that synaptic levels of DA, 5-HT, and NE are increased by methylone[1, 9, 10]. This is qualitatively similar to what is observed for cocaine, MDMA, and several other methamphetamine-related drugs. This supports, but does not confirm or prove, the belief that methylone has similar subjective effects to MDMA, cocaine, and possibly methamphetamine.

DAT/SERT ratios

A common method to classify and predict the likely subjective effects in humans of poorly characterized drugs, such as methylone, on the basis of the limited *in vitro* data described above is to consider the ratio of increased dopaminergic transporter (DAT) and serotonergic transporter (SERT) activities[2]. The ratio of these two activities, known as the DAT/SERT ratio can be used to pharmacologically classify the drug and to predict its possible effects. Drugs with lower ratios (i.e. higher relative activation of SERT) are considered to be more MDMA-like. These drugs are expected to have greater entactogenic effects and reduced stimulant effects, along with a reduced likelihood of addictiveness. Drugs with ratios near 1 are considered to be "mixed MDMA-cocaine-like" and drugs with ratios significantly above 1 are considered to be "methamphetamine-like". As the ratio becomes higher, it is expected that entactogenic effects are reduced and stimulant effects are increased. Also, there is a higher potential for addiction as the ratio increases[2, 8].

Methylone has a DAT/SERT ratio of between 2 and 3. This suggests it is more of a stimulant than cocaine and MDMA and also may be more addictive than MDMA or cocaine[2]. The increased potential of addiction for drugs with DAT/SERT ratios >1 was ignored by Dr. Dudley's report, however may be an important factor for the court to consider, since it may increase the societal impact of methylone. Overall, the DAT/SERT ratio of methylone suggests that it is most similar to cocaine, MDMA, and methamphetamine[2].

Reports on methylone in humans

Data, such as it is, on the effects of methylone in humans is generally anecdotal, often coming from unreliable sources such as blog posts of humans who have tried the drug. For example, one of the drug's inventors, Dr. Alexander Shuglin, describes methylone as having similar potency and antidepressant effects as MDMA, but lacking MDMA's "unique magic"[17]. This characterization seems consistent with other qualitative characterizations found online, which suggest methylone has similar stimulant and entactogenic effects to MDMA, however that the entactogenic effects are less overwhelming[18].

Conclusion on subjective pharmacological effects of methylone

The data described above show methylone's *in vitro* and rat pharmacology is both MDMA-like and cocaine-like. Methylone could also be argued to be similar to methamphetamine in that it has a DAT/SERT ratio > 1, increasing the potential for addiction. The *in vitro* data above also suggests that methylone might function as a hallucinogen and entactogen in humans due to SERT activation.

Anecdotal reports typically compare methylone to MDMA and suggest it is used in place of MDMA. In general, when drawing a direct comparison to a specific drug that is in the Guidelines, the pharmacological literature compares methylone to MDMA. For example, one recent study and review reported that methylone appears to support patterns of abuse which are similar to MDMA, but that further longitudinal data is needed to evaluate this similarity[2]. Thus methylone can be compared to MDMA based on the available data, but can also be compared to cocaine or methamphetamine. The weakness of the available data is discussed in **Part C**. There is ample room for future studies and epidemiological data to reveal that methylone's effects in humans are substantially similar to a variety of drugs, including methamphetamine, MDMA, and either powder cocaine or cocaine base to name a few.

C. Pharmacological Potency of Methylone

To answer: "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."

Summary of pharmacological potency

There is no available scientific data about the effects of methylone in whole humans, so there is no satisfying scientific way to compare the potencies of methylone and MDMA or methylone and another drug in humans. *In vitro* studies using human cells have compared the relative potencies of methylone and MDMA for altering the synaptic levels of specific neurotransmitters through neurotransmitter reuptake inhibition or release. Studies in live rats have compared the potencies of methylone and MDMA through drug substitution. Methylone appears less potent than MDMA in some of these studies, and more potent in other studies. Beyond this, the degree of uncertainty in determining the potency of methylone in living humans, based on *in vitro* and animal potencies is so high that it is very possible that methylone is either much more or much less potent than MDMA.

In vitro studies of pharmacological potency

The available *in vitro* data on methylone pharmacology spans many reports from different labs and can be difficult to compare. In his report, Dr. Dudley contends that two recent studies from respected labs are worth focusing on in particular[9, 10]. The study from Eshelman is particularly significant since it utilizes human cells, rather than rat cells, however the conclusions of the two reports are similar.

These two studies effectively measured the levels of DA, 5-HT, and NE in the synaptic clefts of human and rat synaptosomes and suggest methylone is less potent than MDMA. Table 1 of Dr. Dudley's report accurately represents the data from Eshleman's study. The largest difference between methylone and MDMA from Eshleman's study is found in methylone's SERT activity, which is 17-fold lower than that of MDMA. The SERT activity is believed to be related to the unique entactogenic effects of MDMA. Dr. Dudley uses this data to suggest that the penalty for methylone should be much lower than for MDMA and ultimately proposes a penalty that is 20% of the penalty for MDMA.

It is important however to note that other *in vitro* studies have suggested more similar potencies between MDMA and methylone than Eshleman and Baumann's. For example, methylone has been reported to lead to similar levels of neurotransmitter release as MDMA[8, 9]. These studies also add that methylone has more DA-stimulating activities than MDMA, suggesting it is more likely to be addictive than MDMA, and thus more dangerous. A recent review also suggested that the increased levels of dopamine transmission induced by methylone (as compared to MDMA) increase the odds of addiction[1]. Another study suggested that methylone might induce psychosis at lower doses than MDMA through interaction with the h5-HT2a receptor in a manner similar to LSD[10]. Thus, though the data from Eshleman which was highlighted in Dr. Dudley's report is of a high quality, it does not represent the final word on the relative *in vitro* potencies of MDMA and methylone, let alone their relative potencies in humans. In my opinion, in so far as there is a consensus in the field, the consensus is that methylone and MDMA have similar overall potencies, if somewhat different subjective effects.

Animal studies of pharmacological potency: drug substitution

Dr. Dudley effectively reviewed in detail drug substitution studies of methylone, where rats trained to respond to drugs such as MDMA, cocaine, or methamphetamine, could be made to carry out the same response by administering methylone in place of one of these drugs. The studies reviewed suggest methylone may be on the order of ½ as potent as MDMA. However, as Dr. Dudley points out, interpretation of these studies is difficult and the different experimental designs can lead to very different results. I do not recommend the use of these studies to predict the likely relative potency of methylone in humans.

Insufficiency of available pharmacological data

By necessity, all the available data on methylone's subjective pharmacological effects and relative pharmacological potency come from either *in vitro* or animal studies. Direct tests in humans are unethical for obvious reasons, and methylone has not been around long enough for useful longitudinal or epidemiological data to have emerged that could reveal its societal impact[2]. It is likely that in the long run, it will be epidemiological data, not studies in rats and cells that determine the marijuana equivalency of methylone. In the short term however, the court must make an informed decision about methylone's marijuana equivalency, and this requires consideration of the available data. *To make this judgment, it is necessary to know the degree of uncertainty involved in predicting human potency of a drug from available in vitro and animal studies data*.

If the *in vitro* and animal pharmacological studies described here and in Dr. Dudley's report are highly reliable for predicting potency in humans, then the court may want to alter the marijuana equivalency, either up or down, from that assigned to MDMA. However if the studies lack sufficient information content to viably inform the court's decision, then the court may wish to conserve the 500:1 marijuana equivalency, and neither increase nor decrease it. To give a better idea of the reliability of the types of pharmacological data presented on methylone, three examples are discussed below. 1) The ability of the types of data presented here to discriminate between powder cocaine and cocaine base, which are known to have very different effects in humans and have different marijuana equivalencies. 2) The picture of methamphetamine and MDMA's relative potencies presented by the data in Dr. Eshleman's 2013 study, vs. their actual potencies. 3) The role of direct human testing in the licit drug industry and unreliability of *in vitro* and animal studies for predicting effects of a drug in humans. Each of these examples demonstrates that *in vitro and animal data are very limited in predicting drug effects in humans*.

Powder cocaine and cocaine base ("crack") have very different potencies in humans, but identical *in vitro* potencies

Powder and crack cocaine differ only in their chemical preparation. They are the hydrochloride salt and free base forms of the same molecule, respectively. Thus, the two drugs target the same physiological pathways and both perturb levels of DA, NE, and 5-HT in the same way[14, 15]. Because of this, by definition their *in vitro* efficacies would be identical in the types of studies presented here and by Dr. Dudley. In reality however, because it can be smoked due to its different chemical preparation, crack's onset is much more rapid and intense than that of powder cocaine, which causes crack to be significantly more addictive and potent in humans than powder cocaine[14]. Thus, in the Sentencing Guidelines the powder form has a

marijuana equivalency of 200:1 and the base form has an equivalency of 3,571:1. This demonstrates how *in vitro* data, such as is available for methylone, is insufficient to predict drug potency in humans due to unanticipated effects of chemical preparation or routes of administration.

Methamphetamine and MDMA- *in vitro* data makes them look similar

Dr. Dudley's report focused in particular on the *in vitro* potency data provided by the Eshleman study in 2013, which directly compared MDMA and methylone. This study also included methamphetamine. Methamphetamine and MDMA have very different marijuana equivalencies of 20,000:1 and 500:1 in the Guidelines, respectively (**Figure 1**). Methamphetamine is known to be much more addictive and toxic than MDMA and is a much more serious societal concern, as witnessed to by its more severe penalty in the Guidelines. Despite this, the *in vitro* work carried out by Eshleman revealed similar total *in vitro* potencies of MDMA and methamphetamine, suggesting they would have similar overall potencies in humans. In this case, the same data used by Dr. Dudley to argue that methylone should have a marijuana equivalency of 100:1 instead of 500:1 also suggests that the marijuana equivalency of methamphetamine should be reduced by 40-fold or else the equivalency of MDMA should be increased by 40-fold. If we assume that the available *in vitro* data on methylone could be incorrect by this same figure of 40-fold in either direction, then the appropriate range of marijuana equivalencies for methylone would be anywhere from 2:1 to 4,000:1. This demonstrates the large uncertainty associated with inferring marijuana equivalency based on *in vitro* data. This also demonstrates that the type of *in vitro* and animal based data which is available for methylone cannot reliably discriminate between the effects of chemically related drugs (like methamphetamine and MDMA or methylone and MDMA) which are administered by similar routes.

The licit drug industry: prediction of drug effects in humans requires testing in humans

Unlike the underground designer drug market, licit pharmaceutical companies design and screen new molecules for activity in *in vitro* and animal based assays, with the hopes of eventually testing these drugs in humans and gaining regulatory approval to sell and market the drugs to treat specific pathologies. In vitro and animal based assays are chosen by pharmaceutical companies to try to faithfully imitate and inform on the drug's eventual activity in humans. The incentives for this are two-fold and powerful. 1) There are major ethical and legal pressures not to expose human subjects to potentially toxic drugs, and 2) clinical drug trials in humans are extremely expensive, often costing hundreds of millions of dollars[21]. Thus, pharmaceutical companies are strongly incentivized to maximize the quality of studies carried out *in vitro* and in animals.

The fact that clinical trials of licit drugs in humans are universally preceded by trials in a variety of animals and *in vitro* studies offers insight into the efficacy of *in vitro* and animal studies at predicting drug effects in humans. A recent review in *Nature Reviews: Drug Discovery* highlighted the attrition rate of novel molecules in preclinical, as well as Phase I, II, and III clinical trials in humans (**Figure 2**)[13]. Preclinical trials listed here include *in vitro* and animal studies. Phase I trials directly test safety of the drug in humans, Phase II trials focus on qualitative efficacy in humans (analogous to determining subjective effects in the case of a stimulant like methylone), and Phase III trials focus on potency of the drug in humans.

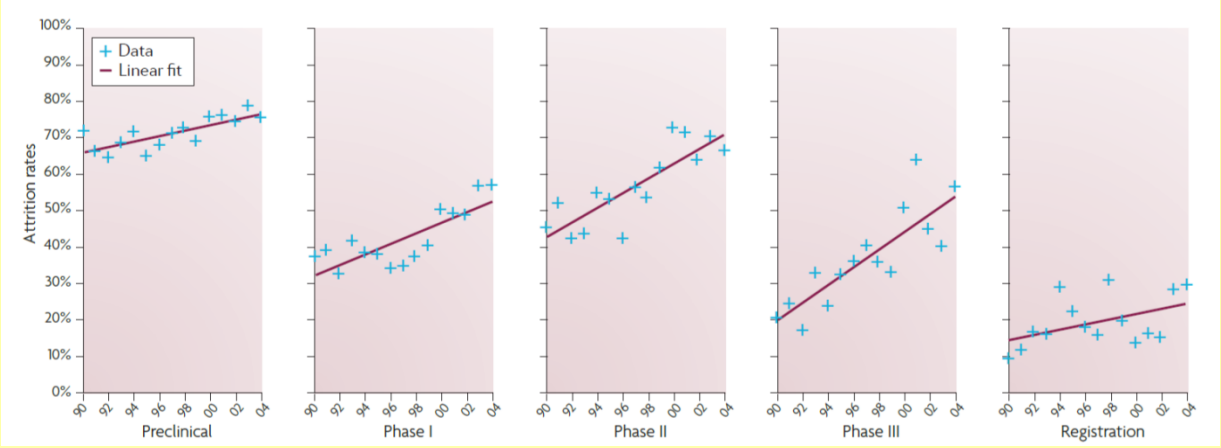

Figure 2. Drug Attrition Rates During Clinical Trials Following *in vitro* and Animal Studies from 1990 to 2004. Figure is reproduced from Pamollii *et al*, 2011[13].

As of 2004, which was the latest data collected for this longitudinal study, the expected success rate of a drug going through Phase I to II was 40%, Phase II to III was 30%, and passing Phase III was 45%. Drugs that fail through attrition at each of these stages generally do so because they failed to fulfil the criteria needed to move on. In other words, drugs that fail in Phase I do so because they are found to be toxic to humans, even though they were safe for animals and *in vitro*. Drugs that fail in Phase II do so because they are found to lack efficacy in humans, even though they were found to be efficacious in animals and *in vitro*. Drugs that fail in Phase III do so because they are found to lack sufficient potency in humans, even though they were found to be potent in animals and *in vitro*. These failures are all despite predictions from preclinical *in vitro* and animal studies suggesting the drug would succeed. Ultimately, this allows estimation of a total success rate of 5.4% for drugs to make it through all three phases (i.e. the mathematical product of the success rate for each phase, 40% x 30% x 45%). This means the failure rate in humans is 94.6% for drugs that have been rigorously and systematically tested in the best possible cell and animal based systems. <u>This demonstrates that cell and animal based predictions of toxicity, efficacy, and potency for a drug in humans are normally wrong, and merely offer a starting point to inform future scientific investigations, even when the animal and *in vitro* studies are carried out in the best possible way.</u>

Conclusion on pharmacological potency of methylone

There are somewhat conflicting studies on the effects of methylone in live rats and in human cells *in vitro*. Methylone is probably less entactogenic than MDMA, but a stronger and more addictive stimulant than MDMA. There is a very large degree of uncertainty involved in predicting drug pharmacology in humans based on *in vitro* and animal studies, as described above. Sometimes what studies omit is as important as what they include. Importantly, none of the studies I found claimed their results could or should be used to predict the effects of methylone in humans. Because of this, there is no sound scientific basis to indicate that methylone is either more or less potent than MDMA.

Vita

I am currently a Postdoctoral Fellow in the Chemistry of Life Processes Institute at Northwestern University. I attained a B.S. in Chemistry from Butler University in 2004, and a Ph.D. in Chemistry and Biochemistry from the University of Texas in Austin in 2014. In 2016 I was awarded a National Research Service Award by the National Institute of Health.

My work currently focuses on the use of bioanalytical techniques to detect and discover new molecules from natural sources like plants, bacteria, and fungi which have the potential to be used as drugs. This work requires a detailed understanding of how chemical structure influences the chemical and biological properties of molecules. In graduate school, I trained in a Medicinal Chemistry lab. My work there focused on bacterial enzymology and on the relationship between a molecule's structure and how it binds to its protein target. This included a detailed investigation of how adding functional groups to a molecule (like a drug) can change how it interacts with its biological target.

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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, Methylone, 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]

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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 steroids[15] 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

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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 marihuana 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

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[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 marihuana 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.

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[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

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[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

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[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.

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[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]

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[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 marihuana 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 marihuana per 1 gram of THC. Under this equivalency, for a given amount of marihuana to contain a similar dose of its primary active ingredient THC, the marihuana would need to contain about 0.6 percent THC.

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

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 marihuana 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 marihuana 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 marihuana 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 marihuana 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 Marihuana; level 30 – at least 100KG but less than 400KG of Marihuana; level 16 – at least 20KG but less than 40KG of Marihuana).

[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 marihuana equivalency of 90,000 kg.; 539kg x 167g = 90,013kg.) If the THC:marihuana equivalency was set instead at the ratio reflecting the best current national data on average marihuana potency, it would be about 1:8. Using the accurate ratio, the marihuana equivalency for 539kg of THC would be 4,312kg (539kg x 8kg = 4,312kg). 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 marihuana 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 marihuana 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.

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[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 Pangourelias*, 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 marihuana 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]

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[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-drugsChinese 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,

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[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 psychopharmocologist. Dr. Curran testified about studies of MDMA that had been done after the Commission's 2001 decision to adopt a 500:1 MDMA-to-marihuana 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.

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[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 study[90] 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

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[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).

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[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,

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[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-Methylenedioxypyrovalerone (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 MPDV-to-.00625gm of marihuana. 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 methyhlone 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 marihuana 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. Synthethic 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

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[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 Table[119] 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

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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).

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[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").

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

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

UNITED STATES OF AMERICA

v. 09CR1136(WHP)

SEAN McCARTHY,
LARRY WARREN HOUGH,
Defendants.

----------x

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

Before:

HON. WILLIAM H. PAULEY III

District Judge

APPEARANCES

PREET BHARARA
United States Attorney for the
Southern District of New York
DANIEL CHUNG
ELISHA KOBRE
Assistant United States Attorneys

MICHAEL SPORN
SCOTT MICHELMAN
JAY RORTY
Attorneys for Defendant McCarthy

JOHN C. MERINGOLO
Attorney for Defendant Hough

(Case called)

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

MR. CHUNG: The government is ready.

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

THE COURT: Go ahead.

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

THE COURT: I have.

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

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

(Pause)

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

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

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

THE COURT: That's fine.

You said there was another matter.

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

THE COURT: That's fine.

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

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

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

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

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

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

neurotoxic, that it causes cell death.

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

We are now prepared to call Dr. Valerie Curran.

Mr. Michelman will conduct that examination.

THE COURT: Very well.

HELEN VALERIE CURRAN,

called as a witness by the Defendants,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. MICHELMAN:

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

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

Q. Could you describe your main job responsibilities in that

role.
A. I am director of the clinical psychopharmacology unit. I am an academic. I have students. I mainly do research. I also am a clinical psychologist and a research lead at the national health service, a series of clinics giving drug treatment to addicts.
Q. Could you describe some of your professional associations and activities?
A. Yes. I am a member of Council of British Association of Psychopharmacology. I am a member of the U.K. Independent Scientific Committee on Drugs. I am a member of several other societies to do with addiction. I am also principal editor of the major journal in the field, unfortunately also called Psychopharmacology.
Q. Could you tell the court what degrees you hold.
A. I have a bachelor's and a master's degree from Cambridge University and a PhD from London University and professional qualifications from the British Psychological Society.
Q. Describe your area of research expertise.
A. My research concerns the cognitive and mood effects of drugs acting on the brain.
Q. Tell us the sources of the funding for your research.
A. Yes. My current funding is mostly government, mainly the Medical Research Council, also the Economic and Social Research Council in the U.K. I also get money, small amounts of money

from various charities, including the Beckley Foundation and the Alcohol and Education Research Council.
Q. It sounds like the bulk of your funding is from the government.
A. Yes, nearly all of it.
Q. Do you have any experience testifying in court?
A. I have only been in court twice, once with a mass litigation for the crown against pharmaceutical companies producing benzodiazepine, like Xanax and Valium, where a large case was taken forward against companies that produced them, and the second case was in the case of drug-assisted rape where again I acted on behalf of prosecution. I have done a lot of legal reports and I also sit on government committees such as the Ministry of Defense Ethics Committee where my expertise on drugs abuse is used.
Q. How long have you researched on MDMA?
A. MDMA, 14 years.
Q. How long have you researched on marijuana?
A. About 12 years.
Q. How long have you researched on ketamine?
A. On ketamine, 11 years.
Q. What types of work have you done on MDMA?
A. I have done studies looking at the variation in the effects of MDMA from the night people take it across the following days. I have done studies looking at the long-term effects of

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

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

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

Q. Describe the nature of your work on ketamine.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Q. No.

A. And the brain imaging later.

Q. Do finish your thought.

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

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

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

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

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

So, scientists reflecting back to 2001, will say those

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

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

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

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

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

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

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

A. Absolutely, yes.

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

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

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

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

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

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

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

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

A. Yes.

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

there might be to generalizing from the animal studies to the human studies, to harm to human beings?
A. With the animal studies you can be sure about causation because you are actually giving them the drug and you give them a placebo. The drawback is, as I was saying, the animal studies before 2001 were all 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 once or twice a month. It's a completely different thing.

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

Some people have argued you can do a thing called interspecies scaling, which is simply an adjustment for weight and it means nothing. You can't do that. You have to equate patterns of consumption. You have to equate how that drug is metabolized. The metabolites differ across different species. I think the 2001 report took that argument which has since been very, very much criticized and no longer holds.
Q. Can you describe the difference between impairment and brain damage.
A. Impairment usually refers to a functional impairment. It's

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

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

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

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

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

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

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

Q. What is a meta-analysis?

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

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

Q. Are there any particularly good systematic reviews and meta-analyses in the field of the MDMA literature?
A. There is one, the Rogers review which looked at the harms of Ecstasy; basically he asked one question, what are the harms of MDMA.
Q. That was one of the papers that you identified and we submitted to the court?
A. Yes.
Q. That was the giant 300-page one?
A. Yes.
Q. Why was that review in particular good?
A. Because it followed the absolute gold standard guidelines for doing a systematic review so, all the criteria for including one study or not including another are clearly laid out and the whole idea is that these reviews are valid, because someone completely indifferent can come along and based on the same information, select the same studies and reach the same conclusions.
Q. Even though it's not a clinical study, its results can be replicated?
A. Absolutely, yes. Its strength is that it takes into account all the studies that have been done wherever in the world and brings them all together and gives a much more powerful way of looking at possible confounds and helping us understand why perhaps marijuana might interact with Ecstasy in

some studies and not others.
Q. In what other ways might the literature be reviewed?
A. The traditional old-fashioned way of doing it was to do what's called a narrative review whereby a person brings together, or several people bring together, things they are thinking about, select studies to include in the review, but don't put down criteria for including them or excluding them. It's more like they include which studies they want and there is no systematic way of reaching conclusions from that because there is nothing laid down in advance. So they are very whimsical and can be rather biased.
Q. Can you give us an example among the studies that have been submitted to the court of a narrative review of the type you describe?
A. Well, Dr. Parrott submitted a review published in 2001 which reviewed 15 years of MDMA research. That's a narrative review. He chose the studies that he wished to include. In fact, there were over 20 of his own studies in there. That's normal; people are a bit biased toward their own work. He also included discussion of papers that were not published, of conference abstracts, all things that would never have been allowed into a meta-analysis.
For example, in that review, Dr. Parrott very nicely lays out a table of all the studies that have shown a memory deficit in Ecstasy users but he didn't also lay out all the

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

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

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

Q. Sure.

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

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

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

A. Yes.

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

A. Yes.

Q. Any others?

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

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

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

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

A. Yes.

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

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

Q. But today there have been?

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

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

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

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

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

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

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

Should I try to explain what statistical significance means?

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

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

MR. MICHAELMAN: Thank you, your Honor.

BY MR. MICHAELMAN:

Q. So, Dr. Curran, could you describe when you talk about a finding of memory impairment as being statistically significant yet also small at the same time? Could you describe what those two things mean and how they can be true at the same time?

A. Shall I do it in terms of -- if we look at the actual research that we have been discussing, the meta-analysis by Rogers and the NextC study, they both concur in showing that the size of the memory effect is roughly -- well, in English, if you were given 30 items to get from a store, so you are going shopping, if you used Ecstasy then you would probably forget one of those items. You would remember 29 out of 30, whereas if you had not used Ecstasy, it is more like 30 out of 30. Those are the effect sizes we are talking about. We are much more used to talking about memory, talking about growth memory with Alzheimer's and things like this. But the Ecstasy users in the Dutch studies were showing such a small effect size, this sort of one word out of 30, that people generally feel that it is not going to impact on day-to-day life.

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

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

Q. Thank you.

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

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

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

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

Q. Could you explain what you mean by that?

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

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

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

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

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

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

THE COURT: Thank you.

BY MR. MICHAELMAN:

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

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

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

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

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

certainly done.
Q. This is "The Harmful Health Effects of Recreational Ecstasy: A Systematic Review"?
A. Yes.
Q. The copy I have says 2009.
A. Yes. It might well be, but the studies included in it only go up to 2006 or 7 because you have to take a cut-off before -- it is a massive amount of work to do a systematic review, and you have a cut-off date, and you will find it is 2006.
Q. That makes sense.
Let's look for specific outcome. Does any study show a persistent damage over time after a user abstains from Ecstasy?
A. Well, in terms of the neuroimaging studies, Reneman, who is a top brain researcher in Amsterdam, did a review in 2006 and four out of five studies at that point showed recovery in terms of serotonin in the brain. And since then, there have been another five studies, all showing recovery either with stopping or recovery less steep as people have reduced their dose. I cannot remember the one study in the Reneman review that hadn't shown it. I think it is nine out of ten have.
Q. So, in general, somebody could use Ecstasy for a period of time, stop use and their brain would, more or less, return to normal?
A. I don't think their brain was abnormal to begin with, it

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

trouble with law -- those kinds of things.
For abuse, you only need to tick one of those and for dependence you need to tick three. And we know that with Ecstasy that people increase the dose they take over time so that if they started off taking 75 milligrams, a year later they might be taking 100. So that is seen as evidence of tolerance. The other way tolerance is seen is you keep taking the same dose but the effect reduces. So you would tick off boxes for Ecstasy. We know the same thing happens with alcohol. If you take the first time you had a beer, it was probably when you were -- you got to be 21 here -- most people would have a beer at 16. A small amount of beer then would have had quite a big effect, and a couple of years later, you probably take twice the amount. So tolerance is something that happens with all drugs and the new DSM V will remove that as being such a major criterion.
Q. You have suggested today overall in your testimony that the harms of MDMA are, though statistically significant, fairly minor. Are you aware of studies since 2001 that disagree with you, that find greater harms than you have attributed to MDMA today?
A. Yes. It would absolutely be the odd study here and there. There is some strange study in Hong Kong where they showed big differences, but I think that was an outlier.
So you are asking me, are there studies that disagree

that the effects are small?
Q. Right.
A. You have to understand that in this field there is a huge variation in the quality of studies. Some studies are published in journals that are not very high-ranking and those studies are often most confounded. But if you concentrate on the quality publications, the quality studies, then I think you never say scientists will agree, but I think that there is a consensus, certainly, that we don't now see MDMA being as impairing -- as we all worried about actually in 2001, and we did worry about the studies that were available at that time, but now we can look back with a much more informed view.
Q. And just to re-emphasize, when you say that some of the studies showing harm would be confounded, you mean not controlling for key variables?
A. For all the important variables.
Q. You spoke about your own view. It sounds like your own view has evolved since 2001?
A. Yes, because part of the reason that my own work went into the direction of looking at what happens to people when they stop using the drugs was based on the same squirrel monkey study by Ricaurte in 1999, which is a real concern for that review where they have given squirrel monkeys huge doses of MDMA in the way I said before, so twice a day for four days, injected into the monkeys. And what they have done is they

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

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

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

A. Yes, I have read it.

Q. And how did you become familiar with it?

A. Because you sent it to me.

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

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

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

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

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

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

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

A. Yes.

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

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

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

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

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

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

used MDMA.
Q. For the record, the Kish study to which you refer is the study in Brain in 2010?
A. Yes.
MR. MICHAELMAN: I will just point out for the Court's benefit that that is one of the studies that the government submitted to the Court in advance of this hearing.
Q. Getting back to the 2001 report, it mentions fatalities, and you said that MDMA does cause deaths?
A. Yes.
Q. Can you remind us how often it does that?
A. Well, I have the U.K. figures, because the U.K. and U.S.A. figures don't compare because we have different coroner procedures.
In the U.K. there are 10 deaths a year that are known to be due to Ecstasy, compared with 22 a year to cocaine and 187 a year to heroin and 150 to cycline. So, yes, it does cause death, but it is relatively rare. And we know what the problem is. When it does result in death, it is generally due to hyperthermia or overheating and heat stroke. And there is one other cause is hyponatremia where sodium levels drop in the blood and that is largely because people have got very hot and drunk too much water and they have swelling in the brain.
Q. The report claims a damage to working memory. Has that been borne out by the subsequent science?

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

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

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

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

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

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

Q. On page 18 of the report it says that MDMA may produce a dysphoria which I take to be a depression, again citing the work of Carl Jansen. Is that claim well founded?
A. I think at that point in the report it was saying that MDMA can be addictive and produce dysphoria. And it cites this paper by Jansen which I am sure they have not read because it is a terrible paper. It has three cases of people they claim to be addicted to Ecstasy.

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

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

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

So to me, none of those speak to -- those are problematic people, individuals who need help. Ecstasy is just one of the issues. They all have horrendous problems.
Q. So I take it then from what you said, what you told us

already today that would not be considered a well controlled study?
A. That would not be considered a study. It wouldn't get into the tabloids.
MR. MICHAELMAN: Just for the record, this is the paper "Ecstasy (MDMA) Dependence" by Carl Jansen, 1999.
And for the record, I point out to the Court that that was one of the studies submitted to the Court by the government.
BY MR. MICHAELMAN:
Q. So speaking generally now, in hindsight, how would you characterize the conclusions in the MDMA report by the sentencing commission in 2001?
A. The conclusions they made?
Q. Yes.
A. They concluded that MDMA was worse than cocaine because it was neurotoxic, and I think now we can reconsider that and, also, we know that cocaine can be addictive where MDMA, I have never seen any addict so I don't think it is possible, but there will be always be some crazy drug users who uses all sorts of drugs, but I don't think that MDMA is addictive.
The other conclusion they were saying was because it was marketed to young school children. I think the problems -- certainly in the U.K. use of Ectasy has gone out, as in Europe. I think it has gone down a bit in the U.S. I haven't checked

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

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

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

MR. MICHAELMAN: I will rephrase.

THE COURT: Very well.

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

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

Q. Thank you.

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

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

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

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

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

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

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

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

long-terms of heavy ketamine use are really horrendous.
Q. Could you describe the effects briefly of marijuana or cannabis?
A. Marijuana, cannabis is a very variable thing and contains a lot of different things depending on where you are in the world. But in general, it is well known that cannabis will impair memory, both acutely and, to some extent, in the long-term in a similar way to what we have been talking about with people that use Ecstasy. But, clearly, cannabis, like ketamine, used daily and heavily can produce a dependence that is different from MDMA in that regard. And cannabis has other harms if people are smoking joints because you get often not only chemicals in marijuana, but it is often also rolled in tobacco. You can get respiratory problems.
Q. How would you compare the harms of MDMA to the harms of marijuana and ketamine?
A. MDMA is certainly not as harmful as ketamine for all of the reasons I just outlined. MDMA and cannabis, well, MDMA doesn't cause dependence where cannabis can, though most people use cannabis recreationally not heavily. So probably they are similar in terms of harm.
Q. Are there any studies supporting the conclusion that MDMA is not more harmful than either of the other two drugs?
A. Well, there have been studies where they have used something called multidimensional analysis to look at to try to

get a way of comparing all drugs together or all illicit drugs.
I know there was a recent paper in The Lancet which is the top medical journal showing a U.K. effort to do this where they rated, using techniques that an American called Larry Phillips used, and he is a behavioral economist who basically provides his work for financial organizations and issues like where to fight radioactive waste control. And they use this multidimensional scaling to have a whole bunch of experts rate 20 drugs for, first of all, harms that each of those drugs do to the individual; and, secondly, harms that it does to society.
And on the scales of those 20 drugs in terms of harm to the individual, Ecstasy is ranked 17th out of 20, so three from the bottom, in terms of harm to the individual. The top three, as you would predict, are heroin, crack cocaine and methamphetamine.
In terms of harm to society it is even lower. It ranks 18. So it is well below marijuana and ketamine and cocaine -- well below that. It is also well below methadone which is a major treatment for heroin addiction with which it ranks equally with the marijuana equivalency tables.
Q. Do these result that you are just describing in The Lancet study, are they confirmed?
I'm sorry. Let me start again.
Have any other papers reached similar conclusions?

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

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

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

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

THE COURT: Go ahead.

BY MR. MICHAELMAN:

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

A. Yes.

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

A. Yes.
Q. I understand you to have testified that in the 2001 report by the U.S. sentencing commission, the harms of MDMA were overstated?
A. They probably reflect what was known at the time, but looking back on them now, yes, they were overstated.
Q. And I heard you to testify that MDMA is less harmful than ketamine?
A. Yes.
Q. And that MDMA is no more harmful than marijuana?
A. That's right too.
MR. MICHAELMAN: Thank you very much.
THE COURT: Let me suggest we take a 10-minute recess and then, Mr. Chung, you will proceed with cross-examination.
MR. CHUNG: Of course, your Honor.
THE COURT: We will take 10 minutes.
Dr. Curran, you can step down.
Be back in 10 minutes.
(Recess)
THE COURT: Cross-examination.
MR. CHUNG: Yes.
THE COURT: Go ahead.
CROSS-EXAMINATION
BY MR. CHUNG:
Q. Good morning.

A. Good morning.
Q. Professor Curran or Dr. Curran -- how would you like to be addressed?
A. I don't mind.
Q. I will go with Dr. Curran.
Dr. Curran, you are the author of a 1997 paper entitled "Mood and Cognitive Effects of MDMA, Weekend High Followed by Mid Week Low," is that correct?
A. Yes.
Q. That was published in an academic journal called Addiction?
A. Yes.
Q. And that journal is what is commonly termed a peer review journal?
A. Yes.
Q. So all of papers that are submitted and published in that journal undergo review by a number of experts in the field?
A. Yes.
Q. In that study -- we are talking about the 1997 study -- you indicated that recreational use of MDMA is widespread, is that correct?
A. It would have been at the time, yes.
Q. So and the purpose of that study was to -- and I am quoting from the article itself -- "examine both the acute and residual effects of MDMA on users' mood and cognitive function," is that correct?

A. Yes.
Q. And a number of human subjects participated in that subject, is that correct?
A. Yes.
Q. The first part of that study was to speak to those human subjects at a dance club, correct?
A. Yes. Or to recruit them, yes.
Q. But you recruited them at a dance club, correct?
A. Yes. It was an unusual set-up because there had been very little work on MDMA at that point. And I found a student who came to me because he was a disc jockey in a rave in north London and I saw the possibility that he could set up a laboratory at the rave and take people off the dance floor, if he wanted, to talk to us and be tested in a controlled way. So that's what we did.
Q. Is it correct that approximately two dozen of those individuals were recruited to participate in the study?
A. Yes. It was a small study. It was one of the first, yes.
Q. Now, a dozen of those individuals reported having taken MDMA at the club, correct?
A. Yes.
Q. And then a dozen others reported having only consumed alcohol at that club, correct?
A. Yes.
Q. You administered a number of tests on those two dozen or so

subjects at the club, correct?
A. Yes.
Q. And those tests were designed to determine their mood?
A. Yes. We were looking at mood and cognitive function.
Q. You first administered those tests at the club in that laboratory setting that you described?
A. Yes.
Q. Then you administered the test again the next day on those same two dozen subjects?
A. Yes.
Q. And then you administered those tests again about three days, again, on those same 24 individuals?
A. Yes.
Q. And you found that the MDMA users, the dozen or so MDMA users had a significantly elevated mood at the club compared to the alcohol only users, correct?
A. Yes.
Q. But significantly lower mood several days later?
A. Yes.
Q. The mood of some of those MDMA users several days later in fact, you said, qualified as clinical depression, correct?
A. What we --
Q. Yes or no. I asked you the question. The mood of those --
A. Yes, yes.
THE COURT: Excuse me.

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

THE WITNESS: Thank you.

THE COURT: You are welcome.

BY MR. CHUNG:

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

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

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

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

Q. Understood.

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

A. Yes.

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

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

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

A. Yes.
Q. You made a presentation at that conference?
A. Yes.
Q. In addition to many other researchers in the field of MDMA?
A. Yes.
Q. And Glen Hanson gave the opening remarks at that conference?
A. Yes, he did.
Q. He was the director of the Drug Abuse Institute's division of neuroscience and behavioral research at the time?
A. Glen Hanson?
Q. Yes.
A. He probably was. I can't remember.
Q. Minor detail.
You know Glen Hanson personally?
A. I have met him at conferences, but I don't know him very well.
Q. Your presentation at that conference was about the effect of MDMA on the body's ability to use tryptophan, is that right?
A. That was a study that I reported there, yeah.
Q. But that is a study that you reported at that conference?
A. And then published, yes.
Q. Tryptophan is an amino acid that plays a part in the production of serotonin?
A. Yes.

Q. It is more popularly known as what makes people sleepy when they eat turkey, right?
A. That's news to me.
Q. I am just trying to provide some context here.
You had conducted research on the interaction between on MDMA and this chemical tryptophan?
A. It was with MDMA users where we challenged them with either enhanced tryptophan, the thing you need in your diet to make serotonin or deplete it, so it was either MDMA users, current, ex or non-users.
Q. Well, thank you for answering my next three or four questions.
That research involved three groups of human subjects, right?
A. Yes.
Q. One group was MDMA users, current users, right?
A. Yes.
Q. And the second group was individuals that had stopped using MDMA for more than one year?
A. Yes.
Q. And, third, individuals that had never used MDMA?
A. Yes.
Q. And all of the study participants, as you had indicated before, were given beverages or drinks that contained a large amount of tryptophan?

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

A. It was being significantly less metabolized than the other two groups.
Q. You also gave the subjects a number of memory related tests?
A. Yes.
Q. Upon administering these tests, you found that the current MDMA users did more poorly than did the non-MDMA users, is that right?
A. I will take your word for it. I can't remember every detail. I think that we found that the ex-users were the ones who were impaired.
Q. This was your study, right?
A. Yes.
Q. The ex-users, like you said, did the poorest on the test?
A. Yes.

(Continued on next page)

BY MR. CHUNG:

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

A. Yes.

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

A. Yes.

Q. Do you remember that paper?

A. Yes.

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

A. Peer review.

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

A. Yes.

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

A. Yes.

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

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

reasons?
A. Yes.
Q. The second group were those who quit for what you call circumstantial reasons?
A. Yes.
Q. Approximately half of those in that first mental health group scored in the range for clinical depression?
A. Yes, in the mild zone.
Q. For clinical depression?
A. Yes.
Q. In that group, the levels of depression and anxiety correlated significantly with the amount of MDMA that these individuals had taken several years previously?
A. In the mental health group, yes.
Q. You stated in that paper that that finding suggested that users may either be more vulnerable to the adverse effects of MDMA or may have had preexisting mental health problems for which they medicated by using, self-medicated by using Ecstasy?
A. Yes.
Q. So two possibilities you mentioned in that paper?
A. Yes.
Q. But you also concluded that a study showed that some ex-users experienced an impairment to mental health that persisted for years after they stopped using the drug, correct?
A. Yes. It would make sense to say that if it was a

preexisting problem.
Q. But that wasn't one of your conclusions, correct, that you found among the individuals that participated in the study that a number of them had mental health impairment years after they had last used the drug?
A. Yes, OK.
Q. Dr. Curran, have you reviewed the expert summary, the document of Glen Hanson that was prepared in advance of this hearing?
A. I read it, yes.
Q. It was a 2-page document?
A. Yes.
Q. Did you review the publications that were cited in that summary?
A. Yes, there was the Degenhardt paper.
Q. One of those papers was authored by a research group headed by Fabrizio Schifano?
A. Yes.
Q. Are you familiar with Dr. Schifano?
A. Yes.
Q. You testified during direct examination that approximately ten people in the U.K. per year die of Ecstasy-related causes?
A. That's right; that's exactly the statistic that's in the Schifano paper.
Q. In the Schifano paper, isn't it correct that the study

found that from 1997 to 2007, approximately 605 people died as a result of MDMA use?
A. No, it doesn't say that in that paper.
Q. It doesn't say that?
A. No.
Q. You testified on direct examination that 99.9 percent of MDMA users use other types of drugs?
A. Yes.
Q. Many MDMA users use marijuana?
A. Yes.
Q. Many of them use cocaine?
A. Yes.
Q. Many of them use methamphetamine?
A. Methamphetamine is quite rare in the U.K.
Q. That's what we have been calling throughout this hearing the polydrug use?
A. Yes.
Q. Polydrug use is what's commonly called a confounding factor when it comes to the MDMA studies?
A. It's one of the confounding factors.
Q. It's a confounding factor that you believe subjects a number of MDMA studies to criticism?
A. Yes.
Q. You agree that out in the field in real life, 99.9 percent of MDMA users are polydrug users?

A. Yes.
Q. You are familiar with Andrew Parrott?
A. Yes.
Q. You are aware that he is, among other things, a professor Swansea University in the U.K.?
A. Yes.
Q. You are aware that he has published over 46 peer review articles regarding MDMA?
A. I never counted; I take your word for it.
Q. You discussed one of those papers during your examination, right?
A. Yes.
Q. A 2001 paper entitled, a 2001 survey of literature regarding MDMA?
A. It was a review, yes.
Q. It was published in the Journal of Human Psychopharmacology?
A. Yes.
Q. That is a peer review journal?
A. Yes.
Q. It's a journal that you yourself have quoted in a number of papers?
A. Over the years, a few.
Q. You consider Professor Parrott's, that 2001 paper whimsical?

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

Q. Obviously you have reviewed that particular paper?
A. Yes.
Q. Are you aware that one of the conclusions of that paper was that although the performance of the group of Ecstasy users that were part of that study is still within the normal range, that long-term negative consequences of MDMA users cannot be excluded? Are you aware that that was one of her conclusions, or one of the researchers' conclusions?
A. I don't remember exactly the discussion but I know the result. The effect of a very well-designed study was that when people, they didn't, the student groups didn't, before they started using Ecstasy, one group started, the other didn't, and when they were retested, the ones who had used Ecstasy recalled half a word less than those who hadn't used Ecstasy.

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

Q. You agree that this was I think you said a well-designed study?
A. Yes, it was a well-designed study.
Q. Bus you don't remember whether one of the conclusions of the Schilt group was that long-term negative consequences of MDMA use cannot be excluded?
A. That doesn't mean anything.

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

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

Q. That's the very same journal in which Professor Parrott's 2001 review was published?
A. Yes.
Q. In that study, the Cotler study, is it correct that the research group conducted a survey of young adult and adolescent MDMA users?
A. It wasn't a survey; I think it was an interview study.
Q. Interview study. These individuals, these young and adolescent MDMA users were interviewed by the research group?
A. Yes. They had a computerized testing system and they offered to people 55 pounds, $55 to come and talk about their use all kinds of drugs. These were polydrug users, I think 40 percent of whom used heroin. So they are not typical of recreational Ecstasy users.
Q. Are you aware that a conclusion of that 2001 Cotler study was that 43 percent of those who were reported Ecstasy use met the accepted diagnostic criteria for dependence according to the DSM-IV?
A. I am aware of that but it's nonsense.
Q. That's nonsense?
A. Yes, it's nonsense.
Q. Are you aware that those results are, that according to the Cotler group, those results were consistent with similar studies in other countries that suggested a high rate of MDMA dependence among users, correct?

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

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

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

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

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

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

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

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

A. Absolutely not.

Q. Absolutely not?

A. Absolutely not.

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

A. Yes.

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

that report regarding the physical effects of MDMA, is that correct?
A. The physical effects?
Q. The effects of MDMA, the harm?
A. The harm of MDMA, yes.
Q. I believe your words were that the commission, you believe that the commission came up with assumptions regarding the physical harms of MDMA?
A. I didn't say anything about assumptions.
Q. That was your testimony, wasn't it?
A. I didn't use the word assumption. I think what I said was that the commission in 2001 was based on the limited evidence that was available at that point, including very high toxic doses of MDMA given to animals.
Q. You recognize that the commission, again from the report, recognized that the potential toxicity to serotonin neurons have been the subject of some disagreement?
A. Yes.
Q. So the commission acknowledged there was controversy regarding the neurotoxicity of serotonin?
A. Yes.
Q. You also recognize that the commission in that report also acknowledged that another point of controversy surrounding MDMA research literature is whether the loss of serotonin sites or serotonin and the corresponding impairment is permanent?

A. Yes.
Q. You acknowledge that the commission realized that there was a controversy among scientists regarding the permanence or the lack of serotonin impairment?
A. Yes. That was based on the study with monkeys showing serotonin depletion of seven years.
Q. At the time in 2001 there was quite of a bit of controversy regarding these potential or actual physical harms?
A. Yes, that was acknowledged.
MR. CHUNG: No further questions.
THE COURT: Redirect.
MR. CHUNG: Your Honor, I don't want to assume certain things, it looks like Mr. Rorty is going to be conducting Dr. Curran's redirect examination. Is that normal practice.
THE COURT: It's not normal. Generally, one counsel conducts the examination of a witness, but do you have any objection.
MR. CHUNG: I don't. It's a sentencing hearing.
THE COURT: Fine.
Mr. Rorty, you have license to conduct the redirect.
MR. RORTY: Thank you.
REDIRECT EXAMINATION
BY MR. RORTY:
Q. I am going to ask you about a number of studies that Mr. Chung just asked you about. Why don't we go in the same

order he proceeded in. Let's discuss the 1997 study regarding recreational use, particularly the weekend high followed by the midweek low; do you recall that study?
A. Yes.
Q. I am sorry, I don't have the full name; can you give us the title of that study?
A. Plus or minus, the last bit, I can't remember the first bit, it was Weekend High Followed By Midweek Low.
Q. Mr. Chung asked you about your finding that survey users when asked about their midweek low reported a condition which was consistent with clinical depression; have I understood that correctly?
A. It was in a very small number of people, mostly in the mild range, but the most important thing is that it was transitory. When we did subsequent studies to go further into the finding, it was only on like day 3 that you find any change in mood at all. By the following Saturday, nobody was depressed; it was literally just a dip a few days after. Dr. Parrott's shown exactly the same thing in a publication. It only lasts for 7 days, it's midweek day or two out of 7 days.
Q. To the extent that users experience symptoms consistent with clinical depression, they experience them for a 2-to-3-day period?
A. Yes.
Q. That's all your study showed?

A. Yes, but on average it's on a very low level of change in mood.
Q. To the extent, what I understand you to say, to the extent they were consistent with clinical depression, it was mild to moderate clinical depression?
A. Yes.
Q. Mr. Chung drew your attention to the conclusions in your study and indicated that it was his understanding that you attributed these effects to, quote, neurotoxicity in that 1997 study.
A. My memory --
MR. CHUNG: Your Honor, objection; that's not a fair characterization of the question and answer on cross-examination.
THE COURT: Put a new question to the witness. I am sustaining the objection as to form.
Q. Did your study conclude that the findings of clinical depression were the result of the neurotoxic effects of MDMA?
A. The conclusion from that study was that either the dipping mood midweek was due to serotonin depletion or to the fact that if you have such a fantastic time, you feel so high and euphoric on Saturday, then anything in comparison is less appealing. But it also said serotonin neurotoxicity cannot be ruled out based on what was known of the animal work in 1996 when I wrote that paper.

Q. Your conclusion with respect to neurotoxicity was not a finding of neurotoxicity --
A. Not at all.
Q. -- but the conclusion that it cannot be ruled out?
A. It can't be ruled out, but to explain both findings, neurotoxicity wouldn't really help because it's only a temporary depletion. Those findings fit much better with animal and human evidence showing after you take Ecstasy on Saturday night, your serotonin levels go whoosh and then up again. I just take that whoosh low and then they are back to normal the next Saturday. It's a transient effect.
Q. To clarify, temporary serotonin depletion is not the same as neurotoxicity?
A. Not at all, no, it's kind of a normal function of the brain in response to lots of drugs.
Q. If I understood the answer you just gave when you said that neurotoxicity cannot be excluded, that was a reaction in part to then-existing animal studies that through the administration of high toxic doses claimed to find neurotoxicity?
A. Yes.
Q. Can you discuss the meaning of the inclusion of a phrase in a study that a finding cannot be excluded? What do researchers take from that? What does it mean to include that finding?
A. It's standard in science and research to try to consider every possible explanation for what you found so every single

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

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

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

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

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

A. No.

MR. CHUNG: Objection.

THE COURT: Sustained.

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

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

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

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

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

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

BY MR. RORTY:

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

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

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

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

Q. A change in the brain does not equate to functional impairment?
A. Absolutely. Functional impairment is more important for a human's life.
Q. In assessing harms which is of greater significance, brain change or damage or functional impairment?
A. Functional impairment. Usually the two go together with most forms of structural brain damage.
Q. Let's apply that to your tryptophan study. My understanding was that you found that tryptophan is less metabolized in ex-users of MDMA?
A. Yes.
Q. Is that a finding that equates to a functional impairment in ex-users?
A. No.
Q. Explain.
A. It's purely, it's only functional impairment; it's just reflecting blood levels of tryptophan which is a standard amino acid that we all need from our daily diet. It doesn't mean that every functional impairment --
Q. To go back to that distinction, your brain chemistry may have temporarily or permanently changed, but it does not change your ability to function in the world?
A. Absolutely, yes.
Q. Let's move to your 2003 study regarding quitting Ecstasy.

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

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

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

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

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

Q. Let me turn to the Cotler study concerning dependence about which Mr. Chung asked you?
A. Cotler.
Q. You discussed her own withdrawal criteria or metric. Explain that. Did I understand that in addition to looking at DSM criteria, she created her own metric for whether or not a person was dependent and specifically whether they experienced withdrawal?
A. Yes.
Q. Was that metric drawn from the DSM?
A. No. In the DSM there isn't, MDMA dependence does not exist, there is nothing in the DSM about MDMA.
Q. Does the DSM contain criteria for dependence on other drugs?
A. Yes.
Q. What other drugs?
A. Most of the abused drugs, heroin, crack cocaine, cocaine, marijuana.
Q. So the authors of the DSM themselves drew a distinction between MDMA and the drugs which have separate dependence criteria?
MR. CHUNG: Objection.
THE COURT: Sustained as to form.
Q. Did the DSM authors draw distinction between MDMA and other drugs in terms of designing criteria for dependence?

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

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

A. About neurotoxicity?

Q. Yes.

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

MR. RORTY: Thank you. No further questions.

THE COURT: Any re-cross, Mr. Chung.
MR. CHUNG: No, your Honor.
THE COURT: I have a few questions.
Following up on this neurotoxicity question, putting aside the now discredited studies by the court, are there not other studies that indicate the neurotoxic effects of MDMA?
THE WITNESS: If you take changes in the axons in animal brains, then lots of other studies show that there are axonal changes if you give sufficiently high doses. I think the key thing really is if you, I mean, as I said before, those are really high doses, a bit like giving a bottle of bourbon a day to a 2-year-old then concluding about the effects of alcohol in normal social use.
The better monkey studies particularly by Fantegrossi and Banks where the monkeys self-administered, first of all, unlike other addictive drugs, over the 18 months, the monkeys could self-administer, they self-administered less over time, whereas addiction is the opposite; they actually self-administer more. But more importantly in both those studies where monkeys self-administered, there is absolutely no change in the brain.
So more and more it's looking like those early pre-2001 studies giving huge massive doses and the studies done since then, some studies even used 20 to 40 milligrams a kilogram in monkeys, of course, you are going to get toxicity

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

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

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

Does that answer your question?

THE COURT: Yes.

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

THE WITNESS: Yes.

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

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

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

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

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

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

THE WITNESS: Ten deaths a year due to Ecstasy.

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

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

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

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

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

THE COURT: It does. Thank you.

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

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

THE COURT: For example, the study Development of a

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

THE WITNESS: That was the Delphic one.

THE COURT: Yes.

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

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

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

THE COURT: Thank you.

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

MR. RORTY: Yes, just one question.

REDIRECT EXAMINATION

BY MR. RORTY:

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

A. 2010.

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

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

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

THE COURT: Mr. Chung.

MR. CHUNG: Just a couple.

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

RECROSS EXAMINATION

BY MR. CHUNG:

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

A. Yes.

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

A. Yes.

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

was an excellent study?
A. Yes. It controlled many more factors than previous studies.
Q. That was a study published in a journal entitled Brain?
A. Yes.
Q. That's a peer review journal?
A. Yes.
Q. You have had a chance to review that paper?
A. Yes.
Q. That paper, among other things, examined the effects on users of MDMA who had used low dosages or what are commonly termed recreational dosages?
A. Yes.
Q. Isn't it correct that you one of the conclusion, I understand that it's a conclusion not the evidence as you distinguished already, that the low dosages of MDMA might cause damage to neurons that are involved in the generation of serotonin, correct?
A. If he said neurons he means serotonin transporters because that's what we looked at.

(Continued on next page)

Q. I am quoting from the paper itself again, Steven Kish, 2010 paper?
A. Yes. He did a PET study so he was looking at serotonin transporters.
Q. "The suggestion that more distal targets of brain stem serotonergic neurons, including the occipital cortex, might be more susceptible to potential toxic damage from Ecstasy is supported by some limited non-human primate data showing that the cerebral, especially the occipital cortex, is more vulnerable to Ecstasy than striatum in terms of the persistence of serotonin reduction."
Do you remember that passage from the article? I know that it was a long --
A. To be honest, no.
Q. But upon hearing that, is it fair to say that one of the conclusions or one of the suggestions from the Kish study is that low dose Ecstasy can have toxic effects or toxic damage on serotonin generating neurons in the cerebral cortex?
A. Not really. Kish actually says that, unlike the earlier studies, pre-2001, his study shows there is no global changes in the brain, that they are very much specified to two areas he showed, the hippocampus --
Q. My question is focused on those specific areas of the brain. I agree with you. I tend to agree with you that he doesn't speak to global change in the brain --

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

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

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

A. Yes.

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

A. The 2010 paper, yes.

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

A. Yes.

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

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

Q. So you recognize that they sat down for one day and then came up with the analysis?
A. Yes. They had previously developed the criteria.
Q. But in terms of analyzing the drugs against this multi-criteria decision analysis, they took one day to do it?
A. It took a lot longer with the advisory council, misuse of drugs, to formulate the criteria on which drugs should be evaluated and --
Q. My question was --
A. In terms of application you are right. Larry Phillips came along and gave a whole day, and people completed the task in eight hours, yes.
Q. Eight hours?
A. I wasn't there, but I presume it was about that -- eight to ten hours.

MR. CHUNG: Thank you.

No further questions.

THE COURT: Anything further, counsel?

MR. MICHAELMAN: No thank you.

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

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

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

I'm sorry. What was the question again?

THE COURT: That study is another survey of experts?

THE WITNESS: Yes.

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

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

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

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

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

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

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

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

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

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

THE COURT: All right. Thank you, Doctor.

Any further inquiries?

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

THE WITNESS: I can't imagine why. Alcohol is a

stimulant in small doses and a depressant in others. I don't know that is relevant, really, to thinking about it.

MR. RORTY: Thank you.

THE COURT: Anything further, Mr. Chung?

MR. CHUNG: No, thank you.

THE COURT: Dr. Curran, you are excused as a witness. You may step down.

(Witness excused)

THE COURT: We will take our luncheon recess. We will reconvene at 2:30.

(Luncheon recess)

(Continued next page)

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.

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

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

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

MR. CHUNG: A brief response, your Honor.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

MR. CHUNG: Understood.

THE COURT: Will the defendants call Dr. Halpern?

MR. MICHAELMAN: Yes.

JOHN HAIM HALPERN,

called as a witness by the defendants,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. MICHAELMAN:

Q. Good afternoon, Dr. Halpern.

A. Good afternoon.

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

A. Yes. I am the director of the Laboratory for Integrative Psychiatry at McLean Hospital and associate psychiatrist at McLean Hospital and assistant professor of psychiatry at Harvard Medical School.

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

A. My main job responsibilities include furthering the research goals of my laboratory which is on the effects of hallucinogens in man, as well as the training of medical students and residents and postoperative fellows and providing clinical psychiatry services within the hospital, as well as private practice.

Q. Could you share any other professional associations or activities?

A. I am a member of the American College of Psychiatrists, and I am board certified in general psychiatry and recently recertified.

Q. What degrees do you hold?
A. I hold my bachelor degree in biological sciences from the University of Chicago, and my medical degree from the State University of New York.
Q. Could you please describe your area of research expertise?
A. My area of research expertise is the use and abuse of hallucinogens and the way in which they are used in a culture. It is mostly focused on the impact of this drug use in humans.
Q. Where do you get the funding for your study?
A. Over the years, the largest amount of money that has come to me has been from the National Institutes of Health and, specifically, the National Institute on Drug Abuse. I have also received money from some foundations and from some private donors.
Q. As the Court is aware, we submitted a draft that is about to be published of one of your papers for the Court's consideration in this case. Where did you receive funding for that study?
A. That study was funded from the National Institute on Drug Abuse for five years, actually, when Dr. Hanson was national director of NIDA.
THE COURT: What is the title of that study, if it has a title at this point?
THE WITNESS: It is on long-term neurocognitive consequences of Ecstasy abuse.

THE COURT: Thank you.

BY MR. MICHAELMAN:

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

A. I have.

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

A. Certainly.

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

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

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

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

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

expert work for the federal government?
A. Yes. I have participated in several workshops for the National Institute on Drug Abuse, twice in one of the work groups that votes on providing grants from the National Institutes of Health, and I have also participated in some development projects for native American researchers that was earlier this year.
Q. When did you begin your work in MDMA?
A. Separate from my training and clinical experience and dealing with people who struggle with substance abuse in terms of research, approximately eight years ago.
Q. What types of studies have you done?
A. So I have spent five years doing a research study looking at the long-term neurocognitive consequences of Ecstasy, from recruiting within a very specific population of all night dance party goers, some of whom use only Ecstasy -- or almost only Ecstasy -- versus people who actually don't use any drugs at all. That is my NIDA-funded study.

And then I have another study in which we are furnishing MDMA in the study as MDMA-assisted psychotherapy as a research tool for dying cancer patients. So I am the principal investigator of that study and I am not actually administering the MDMA myself.
Q. Has all of your work been with human subjects, or do you work with animals as well?

A. All of my work has been with human subjects.
Q. Can you describe the work you have done involving cocaine during your career?
A. Yes. I, again, in addition to my work as a practicing clinical psychiatrist, I administered cocaine source from NIDA looking at the effects of cocaine on the endocrine system and for acute immune response to the exposure to cocaine.
Q. For the record, once again, NIDA is the National Institute on Drug Abuse that you referenced earlier?
A. That's correct.
Q. Dr. Halpern, as you just heard from the argument and the judge's ruling, the government has sought to put before the Court allegations that you lied to the government on two different occasions, one in connection with your application for certification as a Schedule I researcher and second in a proffer session as a cooperating witness. And I would like to ask you about each of those briefly.
Could you explain the circumstances of the incident regarding the Schedule I certification?
A. Yes. I had testified in the grand jury and was instructed by my lawyer to never disclose that I had participated in the proceedings of a grand jury where I might reveal anything that was spoken in there, if it is in a public setting. Sadly, when the field investigators for my Schedule I application asked this -- basically went to this question, it was in a public

setting and I denied and I regret that. I had thought that it would have been clarified up in a private interview, but that didn't happen.
Q. So just to clarify, the field investigators were government field investigators?
A. They were field investigators of the DEA. I was told that I should assume that they are aware of this matter and that they may ask about it.
Q. And who told you that you should assume their awareness?
A. My lawyer.
Q. Then they asked you about your involvement in the investigation and you denied it on the advice of counsel?
A. That's correct.
Q. You said this occurred in a public setting. Can you tell us who else was present when the question was asked?
A. It was asked in the middle of a very busy pharmacy of a hospital, so there are lots of people walking by in a public place. It was not sitting down in a private office, me and the investigators.
Q. Did the study for which you were seeing the Schedule I certification ultimately go forward?
A. Yes.
Q. Did it go forward with you as principal investigator?
A. Yes.
Q. But not with you as the Schedule I registrant?

A. That's correct.
Q. Can you explain how that came to be?
A. In this matter, the DEA is not required to -- there is no deadline of response, and this is a study with dying cancer patients. And while we are waiting to get some answer from the DEA, I even had a couple of potential participants in the study die, so months were going by. So it was recommended to me actually from the DEA office that handles Schedule I registrations that things would move faster if I had one of my colleagues on my treatment team instead apply. And so rather than wait further for an answer, whether it will be approval or an order to show cause, I withdrew my application and one of my colleagues applied and another set of interviews happened and then it was approved.
Q. And his application still named you as the principal investigator?
A. Yes.
Q. And it was granted?
A. Yes.
Q. Since that incident, the federal government has retained you as an expert witness?
A. Yes. To the best of my recollection, I believe that the Eastern District of New York hired me after that incident, yes.
Q. So you are not quite sure about this?
A. Not quite sure at the time.

Q. Fair enough.

Since that incident, the federal government, through NIDA, the National Institute on Drug Abuse, has continued to fund your work on MDMA?

A. It did.

Q. With regard to the second issue, the proffer sessions as a cooperating witness in an investigation, can you describe the circumstances in which the government has alleged that you were dishonest?

A. Yes. It is an extremely scary position to be in. I had the very foolish notion of leaving out information about my childhood best friend, the full extent of my childhood best friend's involvement in that investigation, and so I was not truthful in those earlier -- in those first initial proffer sessions. But I completely regret doing that, and I did make it right and rectified what I had failed to do as originally promised to them. So full disclosure of everything eventually did occur.

Q. And it was, again, after that event that you were retained as an expert witness and continued to be funded by NIDA, is that correct?

A. Yes, that's correct.

Q. Thank you, Dr. Halpern.

THE COURT: Mr. Michaelman, before you move into a substantive area, and I sense you are done with this area of

inquiry at the moment.

MR. MICHAELMAN: I am.

THE COURT: We are going to take a very short recess because I have the privilege of having the chief judge from the bankruptcy court in Chicago in my courtroom, and I am going to say hello to him for a couple of moments.

We will take five minutes.

(Recess)

(Continued on next page)

THE COURT: Mr. Michelman, you may proceed.
MR. MICHELMAN: Thank you, your Honor.
BY MR. MICHELMAN:
Q. So moving to the substance of the focus of the hearing on the harms of MDMA, as I did with Dr. Curran, I would like to ask you to state in summary for the court your conclusions on the main topics we have asked you here to discuss today. Those are the evolution of the field, the harmfulness of MDMA, and the 2001 report. So, taking those in order, could you give us your summary conclusion about the evolution of the field of research into MDMA over the past decade.
A. Since the 2001 report, a tremendous amount of work, research has occurred. That has given us much more information than was available back in 2001. So, yes, that information now informs us that would identify that 2001 report as being out of date and excessively harsh in its conclusions.
Q. Just tick off briefly the ways in which you think the field has changed since 2001.
A. I can think of globally about five different areas in which things have improved since then. We know, we have much more specific and accurate imaging techniques than the type of neuro imaging studies than that occurred back at the time of that report. We have much more data about cognitive function in users and former users. We have information on types of biases that can occur in subjects themselves, so-called stereotypic

threat. People may believe they have been harmed when in objective data they have not.

We have data on knowing that the estimation of dose in animal models was quite excessive back over a decade ago. That has been changed in more recent research. Finally, we now have data on close to 400 human subjects now that have been administered MDMA in clinical research.

Q. Finally, give us your summary conclusion about the harmfulness of MDMA in general, what the current scientific research shows.

A. MDMA can be quite harmful, it is by no means a benign drug, but the risk for harm is modest at best. So a tremendous amount of data in the interim has shown it not to be the type of severely damaging and destructive drug as either described or predicted back in 2001.

Q. Let's go into each of these areas in more detail. To take the changes in the field of research first, you said the field has changed in five ways. I would like to walk you through each of these. Let's start with brain imaging. How has the field changed with regard to improvements in brain imaging technology.

A. The type of compound that's used to identify the serotonin transporter, the way the serotonin is released from neurons in the brain has become much more specific than originally used. The compounds that were used back then are not used anymore.

That's one of the important ways that it's changed.
Q. By back then you mean in 2001?
A. That's correct.
Q. So today, in a brain imaging study we might see things more clearly than we would have a decade ago?
A. That's exactly what I mean.
Q. If I could take you then to the issue of what you call the stereotypic threat which I believe you said was a bias in users to report more harm than can be verified scientifically. Can you talk about what we learned in that area?
A. There are a few different ways this may occur. If you put on an advertisement saying we are going to do a study looking at the harms from Ecstasy, you may get people selecting themselves for volunteering because they have this belief that of course they have been harmed. That may not be reflective of what their real performance is.

In fact, we have seen research done showing that some MDMA users will say that they have memory problems, but then when we objectively test them on this, the types of memory problems they have, we don't realize this. I am referring to the work by Dr. Gillander Bettie and Dr. Harriet Dewitt at the University of Chicago. Dr. Bettie's PhD dissertation in fact was on this.
Q. If we could turn now to the area of cognitive impairment, you had mentioned that had changed as well. What types of

problems were believed to exist with respect to MDMA and cognitive impairment 10 years ago.

A. Quite pointedly, much research was focusing in on verbal memory deficits. That was the phrase that was most commonly encountered back then. So, what we have learned since that time is that some of the verbal memory deficits are actually related to associated mental health problems. People who have psychiatric illnesses like depression and anxiety and untreated, their cognitive performance will be impaired.

Earlier studies did a very poor job of controlling for mental illness, but there are other problems with the research design back then. We heard a lot earlier this morning about the use of confounds, the methodological flaws in the studies. There are numerous ones when it comes to the evaluation of cognitive performance of MDMA users.

Q. Could you list some of those?

A. Some of those types of confounds include an inadequate time from last use of drugs to the time of testing or inadequate control for sleep. Some studies would have these people recruited from all-night raves, frequently partying through the night, we know that sleep impairment or lack of sleep will degrade performance then a comparison group of college kids who are sleeping well or there is no use of drug testing. There wasn't even hair testing used or available back then that we now can employ or the use of screening of the urine from

metabolites in MDMA to control for even immediate recent use of MDMA before testing.

There were quite importantly the majority of those studies were done with very small numbers of people and so the statistical power, the strength of the findings were impaired by having small numbers of people getting a large battery of tests. And also quite concerningly was this strategy of employing polydrug users who didn't use Ecstasy versus polydrug users who did use Ecstasy. Then we are supposed to assume that this complex blending of drug use can be dealt with in this way by comparing polydrug users, ones who have taken Ecstasy and the other group that has not.

Q. Let me follow up on a couple of specific instances. You mentioned the use of hair and urine testing. I infer from what you said that you were referring to researcher's ability to verify the subject had or had not taken the drug within the time they were supposed to have?

A. That's correct.

Q. With regard to the polydrug use, you mentioned that the way of controlling for that in the past was have a polydrug Ecstasy user group and a polydrug non-Ecstasy user group. Today are there are groups that compare Ecstasy users who don't use any other drugs with people who don't use any drugs at all?

A. There have been a few. Dr. Curran mentioned a couple of them, and in addition there is my own NIDA-funded research that

specifically sought out relatively pure Ecstasy users for enrollment.
Q. Then in general, you now named a number of factors that were not adequately controlled for 10 years ago, would you now say that those factors are better controlled in more and more recent studies?
A. Yes.
Q. Moving on to dose, could you explain how the scientific understanding of the appropriate dose to use in MDMA studies has changed?
A. It's now believed that in animal studies, a comparable human dose by bodyweight should be used in these animal studies of approximately 1 to 2 milligrams MDMA per kilogram bodyweight. When you look at animal studies, for example, where that dosage is used, we do not find these same results as were achieved in these earlier studies with doses that's were 40 times greater than that.
Q. You also mentioned the administration of MDMA to subjects in clinical trials. Could you elaborate on that.
A. There have been a variety of studies in which MDMA has been directly administered to human subjects. I believe roughly now about 400 humans have been administered it. All of that any reported serious adverse events or worse in those participants. On top of this in the last year, there is a study published in which MDMA was used experimentally for post traumatic stress

disorder reporting positive results. And there is my study also in which MDMA is administered to human subjects, so far also no serious adverse events or reportable adverse events have occurred.

Q. These have all been FDA-approved studies where they have been in the United States?

A. Yes.

Q. Have they all been in the United States or some in other countries as well?

A. Some occurred in other countries as well.

Q. What's the difference between a neurological change and a functional consequence, a distinction we heard discussed in the earlier testimony?

A. We have neurological changes throughout the life cycle and certainly after medicines are administered that go into our brains, for example. But just because there is a change doesn't mean, brain change does not automatically translate to brain damage. So, when we take a medicine that affects the brain, the function consequence can overall be desirable, but there can be side effects as we know, as I know as a physician, some of which are not desirable. So, both the good results and the bad results are both functional consequences of taking a substance.

Q. When you try to assess the harm of a drug are you looking at whether there has been a change in the brain chemistry

primarily or whether there are deleterious functional consequences?
A. This may come from my focus as a physician. I am looking in terms of clinical health what are the consequences functionally in this person's daily life, in their emotional life, in their work life. That's where the greatest traction is in discussing claimed benefits versus potential harms, particularly if I am working with somebody who has a history of drug dependence and trying to help them evaluate what their drug use is doing to them.
Q. So, in light of all these changes in the field that you have discussed, what does the recent literature show us about the harms of MDMA?
A. The recent literature does identify harms from MDMA use, even death when taken in an excessive amount. That being said, for the vast majority of people who wind up taking Ecstasy, MDMA, illegally the harms appear to be quite modest and time-limited.
Q. Tell us about your own recent paper and what you found, actually, first, your methodology and then your conclusion.
A. So, we have done the study twice. We published in 2006 our pilot data on some 40 individuals, two groups of individuals all recruited from the same all-night dance scene. One group doesn't use Ecstasy or any other drugs. The other group has focused only on using Ecstasy and has had little or no exposure

to other drugs including tobacco and alcohol.

That deals with the issue I mentioned earlier trying to compare these polydrug users, how about we try to avoid it completely. The methods of this earlier pilot study and the later larger one which is the impress manuscript is exactly the same. We also insist on at least 14 days from last drug use at time of neurological testing. Subjects provide a hair sample so we test back for the last 3 months for drug use, including specifically for MDMA. We do a Breathalyzer to make sure they are not doing cognitive testing while there is any alcohol in their system.

We collect a urine sample to make sure there is no MDMA metabolites since it won't show up in the hair if they just took it in the prior three days. That's the purpose of getting the urine test. We also do spot tests for other drugs of abuse at time of neurological testing. We also tested for very carefully on issues of depression and anxiety, a very comprehensive battery of psychiatric evaluation structured and semi-structured in interview form, a neurological exam performed on all individuals.

These were some of the refinements to this work that address a number of the confounds that had been existing in the prior literature. Of course, we are publishing on a much more robust number of individuals too.

Q. What did your work conclude?

A. When you look at comparing the MDMA users overall versus the nonusers, on all of the cognitive tests there are no statistically significant differences. When we split the group of users into two groups, moderate users who have used MDMA 20 up to 55 times and heavier users who have used MDMA more than 55 times in their life, and we compare this to the nonusers, again the moderate users, no differences. On the heavy users, there are only a few measures, some statistically significant, decreases in performance, but they are still globally functioning in the normal rage of cognitive performance.

I might also add that some of those tests there is overlap in some of these cognitive tests. Were it to signify something more ominous, these other tests measures that did not even show statistical significance should, and they didn't.

Q. Are there some studies out there in the field that have shown that MDMA does cause significant harm even after 2001?

A. Yes.

Q. Does the existence of those studies suggest to you that the overall state of the field is in doubt or that the evidence is equivocal about the harms of MDMA?

A. These studies, I think it's important to try to collect them together, take a look at what can we learn from looking at all of these studies in comparison. So we heard a little bit about this from Dr. Curran this morning. I also cited Dr. Rogers' 2009 paper, his comprehensive meta-analysis of

research on the harms from MDMA, and those conclusions overall show that the deficits are rather mild or modest in nature. I agree with that assessment.

Q. If I understand you correctly, you are not saying that there is no debate in the field about precisely what it does, but when the field is viewed as a whole, there is definitely a trend towards the view that the --

MR. CHUNG: Objection; leading.

THE COURT: Sustained as to form.

Q. Are you suggesting that all of the debates regarding the effects of MDMA are settled?

A. I am not. MDMA, I think when we are looking at the type of extreme damage that was described or predicted back in the 2001 U.S. sentencing report to Congress, that there is a fairly strong consensus of opinion that those types of damages are not being realized in the population of users, but there is still ample debate when it comes to where the significance or where we will find these kinds of mild to modest changes. But over the big picture stuff that there is going to be this horrible type of damage, we have got another decade of data that has just failed to realize those types of predictions.

Q. You said a minute ago that some of the early predictions had not been realized in terms of what has been seen in the population. What do you base that conclusion on?

A. If we look at, for example, public health measures that

survey for drug use or emergency room visits, for example, the drug abuse warning network which surveys emergency room visits, we are looking at maybe 15,000 emergency room visits in which MDMA played a role in the last year or two per year in the United States versus I believe 500,000 for cocaine.

When we look at the national household survey of drug use put out by the Substance Abuse and Mental Health Services Administration, we find that the numbers of people that have been using cocaine, the number of people that have been using MDMA, again there is this huge gap. Much more people using cocaine

Q. Does the fact that more people are using cocaine suggest that the emergency room visits that have been documented might be proportional.

A. No, they are not proportional. It's a much greater percentage of people using cocaine are resulting in emergency room visits than the number of people that are using MDMA that result in emergency room visits for MDMA.

Q. So to make sure I understand this right, more people use cocaine?

A. Yes.

Q. And a higher percentage of those people end up in the ER because of that?

A. That's right, in comparison to MDMA, yes. Sorry for the awkward explanation.

Q. Let's move on to discuss the 2001 report. Are you familiar with the 2001 MDMA report to Congress by the U.S. Sentencing Commission?
A. I am.
Q. How did you become familiar with the report?
A. I have a vague recollection of reading it way back when it was issued and of course I reviewed it with great care in preparation for this case furnished from you.
Q. One of the report's main conclusions is that MDMA is more harmful than cocaine. Is that correct?
A. No.
Q. Why not?
A. Cocaine, especially as I have seen from my own clinical experience, this last year, I helped run a partial program for substance abusers in early recovery, people with mental health problems and substance abuse coming to a day program intensively to focus on their substance problems. For a whole year I ran a team doing this. I can't even count how many people I had to work with who had primary cocaine problems, but I can tell you not one of them had a primary Ecstasy problem.
In talking with colleagues and residents' experience, it's quite comparable. With MDMA, we don't find people reporting to emergency rooms and to psychiatric practices seeking treatment for MDMA abuse or theoretical MDMA dependence, but we do with cocaine.

Q. What types of problems would you see in the cocaine users?
A. Well, cocaine users after many years of abuse and heavy use, run the risk of heart attack, of stroke, of death from that, and many other problems, problems relating to having poor nutrition, their mental health and physical health. We can do a standard CAT scan of the brain that can show evidence of strokes in the brain from their repeated longstanding cocaine use. But I have never seen any imaging of an MDMA abuser showing a lesion in the brain attributable to MDMA. I don't know of any publications that show that either.
Q. Then on both measures that we have discussed today, both in terms of the neurological changes in the brain and functional consequences, would you say that cocaine is more harmful than MDMA?
A. Yes.

MR. CHUNG: Objection.

THE COURT: Sustained but next question.

Try not to lead the witness.

MR. MICHELMAN: I understand.

Q. The report says that MDMA compares unfavorably to cocaine because whereas cocaine is a stimulant, MDMA is both a stimulant and a hallucinogen. In your opinion is that a scientifically sound way to compare the two drugs?
A. When I read that statement in the sentencing report, it really made me scratch my head. It almost read like this was

supposed to be some sort of arithmetic; cocaine gets a score of one, it's a stimulant and then MDMA gets a score of two because it's a stimulant and a hallucinogen, one plus one equals two. No, that's not using good science.

Q. Let's return to the types of harms we talked about, neurological changes and functional consequences. Does the fact of being a stimulant and a hallucinogen mean MDMA has greater functional consequences for the user than cocaine?

MR. CHUNG: Objection.

THE COURT: Overruled.

A. No. Merely stating descriptive adjectives to a substance does not by and of itself offer objective proof of danger.

Q. Does the fact that MDMA is a stimulant and a hallucinogen mean that it is likely to have greater neurological consequences for the brain than cocaine?

A. No, it does not.

Q. The report also claims that MDMA is neurotoxic. What do you infer the report means by that term?

A. It was my impression that it meant that axonal death or destruction of a portion of the nerve, of nerve cells.

Q. By this definition from what we know today is MDMA neurotoxic?

A. No.

Q. Explain why not, how we know that.

A. If we give lethal or near lethal doses of MDMA to animals,

you will see damage to the brain, but when you give doses in the range of typical human use, animal studies of 1 to 2 milligrams per kilogram bodyweight mentioned earlier, these sorts of changes are not realized. That's a very critical point. In using human dosing we don't see this type of harm. In fact, we see no differences in these imaging studies and amount of serotonin transporters in the brain. We see, when we do find it, we find recovery. On top of it, these sorts of brain changes are known to occur in a number of medications that have been FDA-approved, such as SSRI antidepressants, for example.

Q. You discussed the importance of getting the dose ratio right. For the court's benefit, I know among the studies submitted to the court, I believe there was one that, I shouldn't lead you, for the court's benefit, were any of the studies submitted to the court ones that dealt with the appropriate dosing level in MDMA studies?

MR. CHUNG: Objection; appropriate dosage level.

MR. MICHELMAN: I suggest witness is an expert and can speak --

THE COURT: Overruled. We can drill down on it depending on what his answer is.

A. Could you repeat the question, I apologize.

Q. Do you recall if any of the studies that were submitted to the court addressed the issue of appropriate dosing levels in

MDMA studies?
A. Yes. The Baumann paper from 2007, I believe focused in very clearly about this issue of 1 to 2 milligrams per kilogram bodyweight versus much higher doses administered, and doses of 1 to 2 milligrams per kilogram specifically stating that the type of harms or evidence of neurotoxicity were not realized.
Q. Why was 1 to 2 milligrams per kilogram an appropriate dose according to Professor Baumann?
A. Because that is approximately the dosage range that most humans consume MDMA.
Q. The 2001 report was also concerned with changes to the serotonin system. Serotonin is something we have heard a lot about today. Can you give your view on whether the report's concerns about the serotonin system have been borne out by the scientific research that has occurred since 2001?
A. Yes. What was predicted back then, this concern that the serotonin system would be permanently damaged, there were public health messages including that maybe people would no longer respond to antidepressant treatment because of this, or there would be a whole generation of people that will be afflicted with depression because of damage to their serotonin system. None of this has been realized in the intervening years, either from direct research, public health surveys, or from my own clinical practice and observation.
Q. Let's talk about some of the other risks in the report.

The report is concerned that MDMA raises the heart rate, is that correct?
A. Yes, MDMA will raise heart rate. So will coffee; caffeine will do that too.
Q. The report is concerned that MDMA induces, quote, a strong urge to repeat use, unquote. Is that finding justified?
A. That finding is absolutely not justified. Their own reference to support that contention was referring to a website www.heroin.org which they themselves in the footnote refer to as offering a compendium of science, pseudoscience and lore, quote unquote. That's the only reference they offered for that contention.
Q. The report itself cited this website and described it that way?
A. That's right.
Q. The related question that was the subject of some discussion earlier, is MDMA addictive?
A. In the classical sense of addiction, no. There may be periods of compulsive use. The vast majority of users do not become physiologically dependent or drug-seeking and go into a lifestyle of drug use and that alters their life forever like we find with cocaine or heroin dependence or alcoholism for that matter.
Q. The report sites concerns about fatalities; do fatalities occur as a result of MDMA use?

A. Yes, fatalities have occurred sadly, but it appears if you look at the number of pills consumed or the number of people using MDMA, even under an illegal situation, very few, very, very few wind up dying.

Q. Then there is a concern with depression discussed a few different times in the report, and they refer to it a few different ways, suicide Tuesday. Does MDMA cause depression?

A. I do not believe MDMA causes depression. In order to make a diagnosis of clinical depression, you must remain clinically depressed for at least two weeks straight. Most of these research studies that showed midweek blues do not ever publish saying there was persistent depression of two weeks' duration, that's one.

Two, my NIDA-funded research, we also inquire very carefully about people's mood after using Ecstasy and the duration of the effect from it, do they get depressed from it, and my next paper will focus on that data. In there, what we found is that people before they ever used Ecstasy, people with histories of depression or anxiety or family histories of depression or anxiety in primary relatives, these are the people almost all of whom will wind up saying they will have a day or two of depressive mood after use. People who don't have that history are much, much less likely to ever even describe post-Ecstasy use as causing depression.

Q. So, in sum, could an objective scientist familiar with the

studies today affirm the report's conclusion that MDMA is more harmful than cocaine?
A. If they are not, if they are aware of all of the current literature that's been published, I don't believe that would be possible for them to reach such a determination.
Q. Could such an objective scientist again assuming familiarity with all of the scientific studies today affirm that MDMA causes brain damage?
A. No.
Q. In sum, would you say the state of the debate has shifted since 2001?
A. Yes. We have a better understanding of the harms from MDMA. There are harms from MDMA. Anything can be used or abused. But the types of ominous conclusions as contained and summarized in that report are no longer accurate.
MR. MICHELMAN: Thank you very much.
THE COURT: Cross-examination, Mr. Chung.
MR. CHUNG: Mr. Kobre will be conducting the examination.
MR. KOBRE: With the court's permission, I would like to position myself over here.
THE COURT: Wherever is going to work best.
MR. KOBRE: Thank you, your Honor.
CROSS EXAMINATION
BY MR. KOBRE:

Q. You have heard of Andrew Parrott, right?
A. Yes.
Q. You are aware that Professor Parrott is currently a professor in the department of psychology at Swansea university?
A. Yes.
Q. You are aware that Professor Parrott is on the editorial boards of several journals?
A. Yes.
Q. That those journals include a journal by the name of Current Drug Abuse Reviews?
A. I was not aware of that.
Q. A journal, Drug and Alcohol Dependence?
A. Yes.
Q. And he is on the editorial board as well of a journal called Human Psychopharmacology?
A. I am now.
Q. An another journal called Journal of Psychopharmacology?
A. Yes.
Q. You are also aware that Professor Parrott has published more than 50 peer review papers specifically regarding the effects of MDMA, is that right?
A. I am not sure because this morning I remember hearing that he was the authorize of 43 such articles.
Q. I don't recall that was what was said.

A. I know he is very well published in his field, yes.
Q. You are aware of Dr. Glen Hanson?
A. Yes, of course.
Q. You are aware that Dr. Hanson is currently a tenured professor in the department of pharmacology and toxicology at the University of Utah?
A. I well remember when he was recruited to the University of Utah after his tenure at NIDA, yes.
Q. He was an acting director of NIDA from 2001 to 2003, right?
A. Yes.
Q. Dr. Hanson has published more than 20 peer review papers specifically regarding the effects of MDMA, right?
A. That sounds about approximately right.
Q. You also heard of Stephen Kish we have been talking about?
A. Yes, the University of Toronto professor.
Q. Professor Kish published in a number of peer review journals?
A. Of course.
Q. Including a journal called Brain, right?
A. Yes.
Q. According to the resume you provided you have published a total of two peer review journal articles specifically about MDMA, is that right?
A. That's correct.
Q. You are in the process of conducting a study regarding the

use of MDMA to treat anxiety in patients with cancer, right?
A. That's correct.
Q. That study involves administering actual doses of MDMA to subjects in a laboratory environment, right?
A. In a laboratory setting, yes.
Q. You are conducting that study in your capacity as a researcher at McLean University?
A. At Harvard Medical School, Harvard University at McLean Hospital, yes.
Q. You have in the past received funding for that study from an organization called MAPS, right?
A. The study of administering MDMA?
Q. Yes.
A. We received a small amount of money to help with the initial protocol design but the actual funding for the study has no MAPS involvement whatsoever. It's funded by one donor, I mentioned private donors, this who I was thinking of, a billionaire benefactor, Mr. Peter Lewis.
Q. You have received, there has been funding for that study from an organization called MAPS, right?
A. That's correct.
Q. MAPS stands for Multidisciplinary Association for Psychedelic Studies, right?
A. Yes.
Q. In fact, you received thousand dollars of dollars from MAPS

in connection with the anxiety study, correct?
A. There were I think approximately thousands but probably not more than $20,000 over the time of that initial time.
Q. You received money from MAPS in connection with other studies that you performed as well, right?
A. The only other funds that I received from MAPS was to help complete data from my NIDA-funded career development ward that took me to the Navaho Nation looking at the long-term cognitive consequences of the religious use of peyote by native American citizens. The bulk of that funding was still provided by NIDA. Some funding was provided by MAPS.
Q. MAPS' public goal is to develop psychedelics and marijuana into prescription medicines, right?
A. That's correct.
Q. In fact, developing MDMA into an FDA-approved prescription medicine is MAPS' top priority?
A. I am not a representative of MAPS, but it's my general impression that's true.
Q. MAPS was founded by an individual named Rick Doblin?
A. Yes, Dr. Doblin founded MAPS.
Q. Doblin is currently the executive director of MAPS?
A. Dr. Doblin is the director of MAPS.
Q. In fact, you have attended various MAPS events with Doblin, is that right?
A. I have attended some of his events, yes. I have spoken at

some of those events, yes.
Q. You attended the burning man festival with Doblin in 2005?
A. It may have been last year but I did go to help as an arranger for the burning man organization, to help with people who have gotten in trouble with their drug use.
Q. That is with Doblin, he was there as well at that time?
A. No, he came at the very end of the event for a few days.
Q. Doblin's publicly professed goal is to help develop legal context for the beneficial uses of psychedelics and marijuana, right?
A. That is I think what you just asked me, yes, the idea is to lawfully and legally explore the development of a substance for its therapeutic prescription purposes, yes.
Q. In fact Doblin publicly advocates the legalization of psychedelics and marijuana for personal growth for otherwise healthy people, is that right?
A. I think that may be his personal opinion.
Q. In order to administer MDMA as part of your anxiety studies, you had to obtain approval from the Drug Enforcement Administration?
A. That was one of many agencies, I shouldn't say many agencies, there is an institutional review board, there is the administrators and senior faculty at the university and the hospital, of course, very importantly, the Division of Public Health of the Commonwealth of Massachusetts.

Q. The reason why you had to secure Drug Enforcement Administration approval was because MDMA is a Schedule I drug, right?
A. Correct. The only lawful way to administer a Schedule I substance in a research setting is to apply for a researcher's registration both from the state in which you hope to perform such research and federally from the Drug Enforcement Administration.
Q. In addition to getting personal approval from the Drug Enforcement Administration, you also, you or the sponsor of the study also had to file a form with the Food and Drug Administration, right?
A. That's correct, and I filed it as an investigator/sponsor and received FDA number 76770 for the study.
Q. The form you filed with the FDA stated that MAPS and its founder Rick Doblin would be the monetary sponsors of the study, is that right?
A. That's not correct. Initially, they hold their own, this is an IND number from the FDA, they hold number 63384 I believe and they can then as a sponsoring agency use that IND number for sponsored research. When we decided to not have MAPS' involvement at all, then I was instructed to file my own independent of MAPS' application to FDA, and that's what occurred for 76770.
Q. What I am referring to is when the form was initially filed

with the FDA, it stated that MAPS and its founder Rick Doblin would be the monetary sponsors of that study, is that correct?
A. That is correct.
Q. You mentioned before that MDMA is a Schedule I drug?
A. Correct.
Q. And Drug Enforcement Administration has classified MDMA as a drug that has a high potential for abuse with no recognizable medical use in treatment in the United States, right?
A. There is a very strange history, of course, behind the registration of MDMA as a Schedule I drug. It was in fact when there were findings of fact by a DEA administrative law judge, it was recommended to be placed into Schedule III and was overruled.
Q. I am asking you is it the case that Drug Enforcement Administration has classified MDMA as a drug that has a high potential for abuse with no recognized medical use in treatment in the United States?
A. Yes, they have classified that. I am sorry, I misunderstood your question.
Q. In 2005, you applied for a Schedule I researcher's registration from the DEA, right?
A. Correct.
Q. You filed that application specifically so that you could perform research using MDMA, right?
A. Correct.

Q. One of the reasons you applied was so you personally could administer MDMA to subjects in the study, right?
A. It was so, yes, I could just do the research that I was trained to do.
Q. Specifically so that you personally could administer that drug to subjects, right?
A. Yes.
Q. Because without the Schedule I registration you could not legally administer the drug to others, right?
A. Of course, that's true.
Q. Without the registration you couldn't even possess the drug legally?
A. I myself personally may not have any physical possession of the substance, that's correct.
Q. You did not disclose on your application for that Schedule I registration that you had been involved prior that he had been previously involved in a Drug Enforcement Administration investigation, right?
A. I am unaware of an application form that asks me to do that. We just fill out a very basic form then there is more specific questions that would occur in a field interview.
Q. As part of the application process as well you were interviewed by Drug Enforcement Administration representatives at your office, right?
A. At my office and on hospital grounds, so in private and in

public places, yes.
Q. That was at McLean Hospital?
A. Yes.
Q. This meeting took place on March 10, 2005?
A. That sounds like the correct date.
Q. At the meeting, a DEA representative asked whether you had ever been involved in a DEA investigation, right?
A. Correct.
Q. You stated no, right?
A. That's correct.
Q. The agent asked yet again, so no one has been asked yet again whether you have ever been involved in a prior investigation?
A. To my best recollection this question was asked once, and as I described earlier, it was asked in this very busy public setting of a busy pharmacy, not in my office privately.
Q. You recall being asked once whether you ever had been involved in a DEA investigation, right?
A. In essence, yes.
Q. Your answer at that time was no, right?
A. That's correct.
Q. But in fact, you had been involved in a DEA investigation, right?
A. That's correct.
Q. In fact, you were not only involved in the DEA

investigation, you were the target of the investigation, right?
A. This is a legal term that I would refer to my lawyer about. As far as I know, it was an investigation for the prosecution of Mr. Picard and the people who were put on trial. But if you tell me that I was, then I will accept it.
Q. The investigation involved an investigation into not only Mr. Picard's criminal activity but into your criminal activity, isn't that right?
MR. RORTY: Your Honor, objection. I would refer the court to the government's proffer with respect to this subject. The proffer indicates Dr. Halpern represented to DEA personnel that he had never been involved in a DEA investigation. The nature of the involvement goes beyond the court's order and indeed the government's own proffer.
MR. KOBRE: The extent of the misrepresentation obviously, one of the major factors is the extent of Dr. Halpern's involvement in that investigation. So, the government would request just --
THE COURT: I am going to permit the witness to answer this question, but we are not going to have a mini trial on Dr. Halpern's involvement in another proceeding.
Do you have the question in mind.
THE WITNESS: I guess repeat it please.
BY MR. KOBRE:
Q. You knew at the time that the DEA investigation that you

had been involved in was an investigation not only into the criminal activity of others, but into your own criminal activity.

A. Not only was I aware of that, my lawyer told me that these investigators that were coming to the hospital would know about it. I was instructed to not disclose anything publicly about what had just transpired in a grand jury.

(Continued on next page)

Q. As part of that investigation, you met with DEA agents on at least seven occasions, right?
A. That's correct.
Q. You not only met with DEA agents, but on several occasions, you met with Assistant United States Attorneys from the Northern District of California, isn't that right?
A. Yes.
Q. One of those several occasions, when you met with DEA was on November 30, 2000, right?
A. I can't recall my memory of the exact date.
Q. On that occasion, you claimed to have no knowledge that Picard was involved in LSD trafficking, right?
A. If that was the first such meeting, I may have stated that. I think I did, and that was not true, and I absolutely made clear that that was a mistake, that was not true to those investigators later.
Q. In fact, on that occasion you told the DEA agents that you had no knowledge that Picard was involved in any criminal activity at all?
THE COURT: Sustained.
Move on to something else.
MR. KOBRE: Just one moment.
THE COURT: Take your time, Mr. Kobre.
Is this an appropriate time to take a short recess?
MR. KOBRE: I am OK continuing, your Honor.

THE COURT: Fine.

BY MR. KOBRE:

Q. Dr. Halpern, you stated on your resume that you received a research grant award from an organization known as the Heffter Research Institute, right?

A. That's right.

Q. And Heffter institute provided support for your research into the cognitive effects of substance abuse in native Americans, right?

A. No, that's not right. They provided funding for my research on the cognitive performance of native Americans who have lawful access to the non-drug sacramental use of peyote.

Q. And the subjects of this study were members of the native American church, right?

A. That's correct.

Q. The study was to determine the cognitive effects of peyote on those individuals, right?

A. That's correct.

Q. And the study ultimately led to the publication of an article, right?

A. That's correct.

Q. And that article was published in 2005, right?

A. That's correct, in a peer review journal.

Q. The Heffter Research Institute is located in Santa Fe, New Mexico, right?

A. Yes.
Q. And one of the goals of the Heffter Institute is developing knowledge regarding the safe use of classical hallucinogens, is that right?
A. I believe so, yes.
Q. In another one of those meetings with the DEA agents, one of those meetings took place on March 26, 2001. Do you recall that?
A. There were so many meetings, but I will take your word that it was on that day.
Q. At that meeting, you told agents of the DEA that you received two grants from the Heffter Institute, right?
A. I think so.
Q. And you told them that the first grant was issued in 1998, right?
A. That sounds right.
Q. And that grant was for $30,000, right?
A. That's correct.
Q. And it was a grant related to your peyote study?
A. That's right.
Q. And peyote is another Schedule I controlled substance?
A. False. False. Just absolutely false. It is a Schedule I drug of abuse and a Schedule I controlled substance for everybody else, but for native American who have limited sovereignty it is not a Schedule I drug.

Q. I did not ask you for native Americans, I asked you if peyote was a Schedule I controlled substance. Is that true?
A. For everybody but the people that are using peyote that I was studying, in that context, it was a Schedule I drug.
Q. And peyote is a hallucinogen, right?
A. For outside of the scope of my research in that matter, yes.
Q. I am only asking you, is peyote a hallucinogen?
A. Yes.
Q. And LSD is hallucinogen, right?
A. Yes.
Q. And MDMA is a hallucinogen, right?
A. MDMA is currently scheduled in the Controlled Substances Act as a hallucinogen but, scientifically, it doesn't meet the full definition of "hallucinogen."
Q. But it has hallucinogenic properties?
A. It has some, yes.
Q. You in fact did receive a $30,000 grant from the Heffter Institute?
A. I did.
Q. And that was in 1998?
A. That's right.
Q. On March 26, 2001 when you met with agents of the DEA, you initially told them that you had no knowledge of the origins of that money, is that right?

MR. RORTY: Objection, your Honor. I believe that this goes beyond the terms of the Court's order and the government's proffer.

MR. KOBRE: Your Honor, it directly goes to another misrepresentation of Dr. Halpern, directly.

MR. RORTY: I would note that in the government's proffer is the description of alleged criminal conduct. That proffer includes acceptance of money from a research agency and describes the circumstances of the acceptance of those funds. In the government's proffer concerning false statements to agents and prosecutors, the description of the false statements is simply the nature and extent of his involvement with individuals who were involved in the manufacture and trafficking of LSD.

MR. KOBRE: And that is exactly where this line of questioning is proceeding.

THE COURT: It is taking on the hallmarks of a mini trial.

Move on.

I am going to sustain the objection.

BY MR. KOBRE:

Q. Dr. Halpern, you yourself have used drugs on multiple occasions, isn't that right?

MR. RORTY: Objection. Relevance.

MR. KOBRE: Your Honor, it goes to bias of the

witness.
THE COURT: Sustained.
Q. Well, Dr. Halpern, you testified before that on March 10, 2005, you met with interviewers from the Drug Enforcement Administration, right?
A. Yes.
Q. And that was in connection with your application to become a Schedule I researcher, right?
A. No, to become a Schedule I registrant.
Q. Correct. Is that right?
A. Yes.
Q. After that meeting, four days later on March 14, 2005, you called a DEA investigator regarding your application to become a Schedule I researcher, right?
A. That's correct.
Q. And that was just four days after the agents had interviewed you at your office, right?
A. Correct.
Q. You had learned by that point that the DEA investigators believed that you had lied to them at the interview, right?
MR. RORTY: Your Honor, I am going to object again, beyond the scope of the government's proffer and covering ground that I believe has been well covered in this examination.
THE COURT: Where are you going, Mr. Kobre?

MR. KOBRE: Your Honor, it goes to bias of the witness. It is not a very lengthy line of questioning.

THE COURT: How is it relevant whether he learned at that point four days later that government agents believed he lied to them at the interview?

MR. CHUNG: Your Honor, if I may?

THE COURT: Go ahead, Mr. Chung.

MR. CHUNG: On direct examination, Dr. Halpern testified that there was a reason for lying, that he answered no to the DEA investigators' question of were you involved in a DEA investigation? His reason, his testimony was that his lawyer had instructed him or advised him that the investigators would know and that he could, in effect, misrepresent to the investigators that he had not been involved in that DEA investigation.

This line of questioning, and it will be a limited line of questioning, is intended to rebut that testimony.

MR. RORTY: I just heard the government proffer that this line of questioning was to bias.

THE COURT: I am going to permit this limited inquiry.

Go ahead, Mr. Kobre.

BY MR. KOBRE:

Q. Dr. Halpern, you had learned by that point that the DEA investigators believed that you had lied to them at the interview, right?

A. Yes.
Q. And during the phone conversation, you tried to convince them that they had misunderstood you, right?
A. Or that I had misunderstood them.
Q. But just several days earlier, as you testified before, they asked you a clear question, have you ever been involved in a DEA investigation, right?
A. That is not the phrase that they used. You are creating a question that they did not ask.
Q. Well, you just testified earlier that they asked you whether you had ever been involved in a DEA investigation?
A. They inquired whether there was an investigation. I don't recall it being asked the way you are phrasing it. So I guess that I should --
Q. Now, in this phone conversation, you tried to convince them that it was all a misunderstanding, right?
A. Indeed.
Q. And you told them that you don't want anyone in the DEA to think that you are not doing what you should be doing, right?
A. There was no reason for me to lie to them or deceive them with the intent of providing them misdirection.
Q. You then asked the interviewer during this phone conversation how high they wanted you to jump? Do you recall saying that?
A. Absolutely. And what I meant by that was that I had every

interest in doing this research by the book.
Q. Now, you then withdrew your application to become a Schedule I researcher with the DEA, right?
A. I eventually withdrew my application for registration, for Schedule I.
Q. And another researcher applied, right, for DEA registration?
A. Correct.
Q. But that was for precisely the same study as you had originally applied, right?
A. Yes.
Q. The research protocols stayed the same?
A. That's right -- no. It was modified to make it extremely, extremely clear that this other investigator would be in charge of all of the responsibilities involving the handling of MDMA and that I would not be.
Q. Right. So the only thing that changed about the study was the name of the researcher?
A. No. The only thing that changed was that that task was then added to one of my research colleagues.
Q. Under the new application, you were not to have any access to the MDMA, right?
A. That's what I wrote, yes.
Q. That's correct?
A. Yes, that's correct.

Q. So the bottom line is, since you do not have a Schedule I registration, you are not permitted to dispense MDMA as part of the study, right?
A. I am not permitted to physically dispense it, but if I enroll a subject in my study, then indirectly I guess I am.
Q. Physically --
A. Physically, I don't want to go anywhere near touching it.
Q. When conducting a drug study, particularly of a hallucinogen, it is your position that the researcher must take the drug himself or herself in order to conduct the research, right?
A. That's not written into my protocol to do something like that, no.
Q. No. I am asking you, is it your position that a researcher, when conducting a study, a drug study, particularly of a hallucinogen, the researcher must take the drug him or herself in order to properly conduct such research?
A. No.
Q. Well, in 2008, do you recall that you gave an interview to a paper called The Phoenix? Do you recall that?
A. I do.
Q. In that interview you discussed your research on the effects of peyote on members of the native American church?
A. Yes.
Q. And in that interview you were asked if you yourself had

ever tried peyote?
A. Yes.
Q. You said you did take peyote and you would not have been able to do the research if you had not, do you recall that?
A. Of course.
Q. Your study regarding MDMA cancer patients was originally funded by MAPS, right?
A. It was initially funded by MAPS.
Q. But MAPS no longer funds the study as you testified before, right.
A. That's correct.
Q. MAPS no longer funded the study because McLean Hospital refused to allow the study to go forward due to the involvement of MAPS, right?
A. During the short tenure of one president of McLean, it was his individual decision to no longer accept funds from MAPS -- one individual, not McLean.
Q. But you couldn't conduct the study at McLean so long as MAPS was funding it, right?
A. That's correct.
Q. As a result, MAPS directed one of its major donors to fund the study instead, right?
A. Yes.
Q. And that study is funded by, as you mentioned before, an individual named Peter Lewis?

A. Correct.
Q. Since 1991, Lewis has contributed $5 million to the ACLU you fight drug laws, right?
A. I have no knowledge of that. I don't know.
Q. Well, Lewis has made large contributions to drug legalization campaigns throughout the United States?
A. I don't follow this man's pattern of donations. I know he is a philanthropist.
Q. You are aware that he has given a great deal of money to MAPS, right?
A. Actually, I am not. The only major donation that I knew that he was going to make was actually potentially to my study, and then he wound up donating it directly to me.
Q. So it is your testimony today that you don't know that Lewis donated money to MAPS?
A. I am sure that he has, I just don't know the amount.
Q. And you are aware that Lewis was chairman of the board of the Marijuana Policy Project?
A. I knew that he had involvement in the Marijuana Policy Project. And the only other thing that I know was that he was the biggest donor to the Guggenheim Museum.
Q. Now you testified earlier that you have written a total -- not written -- you have published a total of two peer review journal articles specifically concerning MDMA, right?
A. I have also published -- yes, yes.

Q. Specifically --
A. Peer review or journal articles?
Q. Peer review journal articles?
A. Yes, two.
Q. One of those studies was published in 2004, right?
A. I believe so.
Q. That was your initial study regarding MDMA, right?
A. I think it was 2006.
Q. And the other, there was another study that has not yet been published about MDMA that we talked about earlier, the 2010 study?
A. Correct.
Q. And the 2010 study is entitled "Residual Neurocognitive Features of Long-term ecstasy Users with Minimal Exposure to Other Drugs," right?
A. Yes.
Q. And your 2004 paper was entitled "Residual Neuropsychological Effects of Illicit MDMA in Individuals with Minimal Exposure to Other Drugs," right?
A. Yes.
Q. In your 2010 study, one of the tests used was called revised strategy applications test, right?
A. Yes.
Q. That is the RSAT?
A. Yes.

Q. You found in your 2010 study that Ecstasy users had a significant deficit on that test, right?
A. They had a statistically significant difference.
Q. Well, you concluded in that study that the proportion of "brief items on the RSAT was strikingly and significantly lower in heavy Ecstasy users," is that right?
A. That's right.
Q. Your 2004 paper states that it provides evidence that "heavier and/or more prolonged MDMA use may be associated with residual cognitive deficits," correct?
A. That's right.
Q. In your 2004 study, the median lifetime episodes of MDMA use among the MDMA user group was 60, right?
A. That sounds correct.
Q. In your 2010 study, the median lifetime episodes of MDMA use in the MDMA user group was 43.5, right?
A. That's right.
Q. So the median lifetime episodes of MDMA use among MDMA users was nearly one-third less in your 2010 study than it was in your 2004 study, right?
A. That's correct. It sounds right.
Q. Now, in your 2010 study, the median number of days since last Ecstasy used when tested for the Ecstasy user group was 121, right?
A. Correct.

Q. In your 2004 study, the median days since last Ecstasy use when tested for the Ecstasy user group was 65 for heavy users, right?
A. That sounds correct.
Q. So the median days since last Ecstasy use when tested for the Ecstasy user group in the 2010 study was approximately half that in the 2004 study, is that right?
A. Yes.
MR. KOBRE: Nothing further.
THE COURT: Redirect examination?
MR. RORTY: I have no questions on redirect.
Thank you.
THE COURT: I have a couple of questions.
What are the neurological physical effects of cocaine as opposed to MDMA?
THE WITNESS: Well, I think the most glaring example of contrasts would be in evidence of stroke, of lesions in the brain that can be visualized on an imaging. Cocaine is basically constrictive; it will cut off the supply of blood. And through heavy and excessive use, this can actually cause tiny strokes that wouldn't even be known by the patient over time, but through many, many years of use, you will see that on imaging, you will see that a lot of these heavy users -- and this sort of thing is not found in MDMA users.
I also did neurological examinations of subjects in my

NIDA funded study because of concerns of these early claims of Parkinson's like disease or abnormal movements in Ecstasy users, and so I thought it would be important to do a neurological exam on all of these people to see if I could illicit that, and I didn't on any of the subjects in the study.

THE COURT: How do the harms of marijuana compare to MDMA?

THE WITNESS: I think the harms from marijuana come quite often because people who get into problem use, it can persist and become daily users, repetitive users, heavy users. Many patients that would become marijuana dependent and smoke daily for decades, but I have never met any patient who abused MDMA, Ecstasy come to me and say, oh, yeah, I have been a daily user of MDMA for the last year. So that is the difference in types of problems from it.

I think what makes it so hard to compare one drug with another is the pattern of use, pattern of abuse, the dosage range that they use. In some ways, we could say that MDMA is more dangerous than marijuana, for example, the dose predicted to be lethal in marijuana is much, much higher than it is with MDMA. It is only theoretical in marijuana. It is estimated to be eight kilograms consumed at once. So I don't think that there are any cases in the literature of marijuana overdose cause of death but, of course, we do have that from Ecstasy.

So depending on what part of the toxicity we are

looking at, what part of harm we are looking at, one may be perceived as more potentially dangerous than the other, but I believe Dr. Curran drilled down to what would be the most accurate assessment, that for the majority of users consuming MDMA on one or two times a month, it is probably much less dangerous than the chronic consumption of marijuana.

THE COURT: It terms of the trend of MDMA use, can you characterize what your studies have revealed between 2001 and today?

THE WITNESS: Thank you for asking that question, because when I originally proposed my study to the government, there was a large scene of Ecstasy exclusive users in the Greater Salt Lake City area and by the time of my funding, my case finder who I worked very closely with, couldn't find the same abundant number of people. It made it much harder.

So I had promised NIDA that we would get over 200 subjects, but my final data set, that is the one that is in the Impress paper, and you will notice that the number is smaller because this population dried up. It was much harder to find them. So by that measure, the trend, I directly experienced in the collection of this data was that the use actually went down.

THE COURT: To what do you attribute that?

THE WITNESS: In part, it has to do with the social mores of the area. We heard earlier testimony that 99.9

percent of Ecstasy users are polydrug abusers. And here you have a study of a number of people that are pure Ecstasy users.

Salt Lake City is the headquarters of the Church of Latter Day Saints, and it is very clear that the use of alcohol is forbidden, and drugs like marijuana have been clearly forbidden. And this filtered into the mores of the culture of the area.

I actually interviewed people born and raised atheists, but their parents and themselves have never even tried alcohol once in their lives, and this happened a number of times -- something that I think I very rarely encountered elsewhere in the country. But it was quite a public campaign against MDMA, and it became quite clear that MDMA is forbidden. It was not on the forbidden list for the Church of Latter Day Saints for a long time and then it was. So the experience and the instructions to stay away from this drug was better absorbed by the community. I think that was one part of the reason why it changed.

THE COURT: Are you familiar at the current time with what the national trends are in terms of the use of MDMA?

THE WITNESS: I am.

THE COURT: What are they?

THE WITNESS: There is very good year-to-year surveys that come out of the University of Michigan, Monitoring the Future Study which is funded by NIDA. And what we see is a

trend of modest use amongst teenagers. Look at the Sanchez study, the national survey of drug use, the use of hallucinogens has been low or stable. In some years it trended up a little bit, but it has never grown exponentially year to year.

THE COURT: Earlier on, I think on cross-examination, you described MDMA as being on Schedule I as a hallucinogen. And you said it had some hallucinogenic properties. What is the distinction, if any, that you are drawing there?

THE WITNESS: The important one is that when people take what we term a classical hallucinogen like mescaline or LSD, there is a loss of control, a loss of ego-control, this dissolving of sense of self. This does not occur under the use of MDMA. So people under the influence of MDMA are still aware of who they are, and the type of impulsivity that they do is not based on that they have lost their sense of self. This does occur from classic hallucinogens. It does not occur with this drug, MDMA.

THE COURT: Is there a debate today among researchers as to whether or not MDMA is in fact a hallucinogen?

THE WITNESS: I think there is a consensus that the use of either empathogen -- or entactogen is the more accurate term -- and when we look at peer review publications, I think we will see a trend year to year of more use of that term. It is very difficult in this field to use the term "hallucinogen"

in and of itself because even the drugs that are labeled classical hallucinogens do not induce hallucinations typically, so this definition is one that is wrought with a lot of complications. But, scientifically, we are still labeling it this way, even though we understand it is not very accurate.

THE COURT: In looking at the paper that you are about to publish, you find little evidence of decreased cognitive performance in MDMA users, correct?

THE WITNESS: Correct.

THE COURT: But you also state in that paper -- and I am quoting now, I think, "This finding contrasts with many previous findings including our own."That suggests to me that there is an ongoing debate and no clear consensus, but would you comment on what you meant there?

THE WITNESS: When we were referring to other research, we really were referring to much of what you heard in my testimony today which is that the type of excessive deficits that were reported in small studies not found. And when we were referring to ourselves, we are referring to the one earlier publication in which we found deficits suggestive of impulsivity on the Revised Strategic Application Test where we did not replicate those findings.

Those results, by the way, on that one specific measure are all within the range of normalcy. The test was actually designed for people with traumatic brain injury, so we

don't even have a good sense of when this type of test is applied in drug abuse. It is a relatively test. It is a task demanding task. I can quickly tell you what it is. It is hard to do.

You are given only 10 minutes and you have one pile of papers where you have to add up the number of items, another pile where you have to draw a copy of a complicated diagram and, a third pile where you write down like a phrase that's above it. And if on any given page, if you see a frowny face, you are not supposed to write anything on that page. And we tell you that whether the task is easy, moderately difficult or very difficult, they are all going to be scored the same, go. You will see papers flying all over the place.

The point is to see if can you figure out the strategy that is going to get you to do it the best. Part of the trick -- we don't even tell people -- the first two pages that you do, we are not even going to score it. You see some people carefully filling out the first few pages, and they are not getting what needs to be done to get the highest possible score.

So in an earlier study with a much smaller number of individuals, some of the heavy users did worse. And we thought it was an example of impulsive decision-making and not the best strategy. And we are still left thinking it may be that these very heavy users, that there was something impulsive about them

to begin with probably before they ever took the Ecstasy. And that's whether the limitation would work, so we want to repeat this test more in this population.

THE COURT: This morning we talked at length about David Nutt's studies, and what is your assessment of those studies by David Nutt?

THE WITNESS: I believe I also cited the 2010 paper to the Court also. I think Dr. Nutt's report is quite relevant because it is not just a collection of talking heads voting their opinion. These are all very serious scientists that had to think very carefully about how we were going to fill out these measures when they came for the actual gathering.

Rather than go with the prevailing desired opinion probably for a man in his position, he bravely forged ahead and let the chips fall where they may -- what a good scientist should do -- and he paid the price of losing his position even for just stating the facts as he clearly saw them with his colleagues. I think it is a very important paper for the Court to consider.

THE COURT: How does the age profile of MDMA users compare to other drugs such as cocaine, marijuana or methamphetamines?

THE WITNESS: I think most people who have taken Ecstasy have tried marijuana, in general, before MDMA. And so an older group of people are using MDMA -- late teens, college

years, early adulthood, and then the use tapers off. So it is much more unusual for me to interview people in their 30s or 40s who have used MDMA. But marijuana use may persist, and those that start using cocaine and methamphetamine, well, it won't matter at what age they start, if they are using it, they will quite often relapse to it later in life too.

THE COURT: The sentencing commission in its report reflected the fact that MDMA was targeted at the youth. Do you agree with that?

THE WITNESS: I don't agree with that. It appears to be a misunderstanding of the subculture of these all night dance parties. In 2001, there was a tremendous amount of public outcry and Anti-rave Act came out. The term "rave" was something new. Obviously, dance parties will attract younger people. And yet unlike other drug using populations, this group of users welcomes non-users. So for me to do this study that we have heard about today, to find a large group of people who don't use any drugs at all is remarkable in comparison to my experience of using other drug using people.

For example, I handed out flyers at one of these all night dance parties to try to get people to come to my study and I saw this young man dancing with glow sticks and looking wrapped up into himself. And he shows up at my study, and I thought, for sure, this is an Ecstasy guy. And it turns out that he just came back from mission. He has never used any

drugs in his life, but he just loves dancing and he loves being accepted from people that are different from him. I will never forget that, because I am not used to seeing that when I have worked in detox centers and longer-term residential programs for drug abusers. It is different. It is what is attracting people is not the Ecstasy use, it is the entire environment that they are enjoying.

THE COURT: Thank you, Dr. Halpern.

Do counsel have any questions that they would like to pose in light of the Court's inquiry of the witness.

Defendant first.

Mr. Michaelman.

MR. MICHAELMAN: Yes, your Honor.

THE COURT: Why don't you stand up and take the podium.

REDIRECT EXAMINATION

BY MR. MICHAELMAN:

Q. Dr. Halpern, the judge asked you about your discussion of the discrepancy between a couple of different studies that you yourself noted in the 2010 paper. Could you characterize the extent or the range of the debate among different studies? How big of a disagreement are we talking about here in terms of studies of cognitive impairment?

A. The disagreement is over the types of mild decreases in cognitive performance whether or not -- they may be

statistically significant, but are they functionally significant, just in that sphere? I think, in general, there is consensus that there is evidence of severe brain damage now. There is no debate about that anymore. We are just not seeing that. The debate is in the area of these mild performance decrements that do not appear to be functionally significant.

Q. We have heard today and in questions asked by the government that there was some acknowledgment in the 2001 report that there was some debate even then. Would you compare the range you have just described about the debate about cognitive impairments from MDMA? Can you compare that to the type of debate that might have been going on in 2001?

A. Yes. Very clearly, the debate as presented in the report, I think they are to be commended for acknowledging that type of debate, but that debate does not exist today. The evidence of severe neurocognitive impairments, I think that you can see it in the comprehensive meta-analysis report of Rogers of 2009. It just doesn't hold water anymore. It is not like that anymore, that extensive range of debate.

MR. MICHAELMAN: Thank you, Doctor.

THE COURT: Mr. Kobre.

MR. KOBRE: Just briefly.

THE COURT: Go ahead.

RECROSS EXAMINATION

BY MR. KOBRE:

Q. Dr. Halpern, in your 2010 paper, your criteria was designed to exclude non-Ecstasy drug use as much as possible without being so strict so as to excessively reduce the participant pool, right?
A. That's correct.
Q. Now, most Ecstasy users use other drugs as well, right?
A. Yes, that's true.
MR. KOBRE: Nothing further.
THE COURT: Anything further, Mr. Michaelman?
MR. MICHAELMAN: No, your Honor.
THE COURT: Very well.
Dr. Halpern, you are excused as a witness. You may step down.
(Witness excused)
THE COURT: Do you have another witness here at this juncture we can get started?
MR. RORTY: Your Honor, the defense has no further witness. I assume that question was addressed to the government.
THE COURT: It was addressed to both parties. I was certainly was under the impression that the defense has no further witnesses.
Does the defense rest?
MR. RORTY: Yes.
THE COURT: Does the government have witnesses to

call?

MR. KOBRE: Yes, your Honor.

We call Professor Andrew Parrot.

THE COURT: We will work until 5 o'clock, and we will resume.

Is that acceptable to the government?

MR. KOBRE: Yes, Judge.

THE COURT: And to the defense?

MR. RORTY: Yes.

ANDREW CHARLES PARROTT,

called as a witness by the government,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. KOBRE:

THE WITNESS: I am Andrew Charles Parrot.

I am a professor at the University of Swansea in the United Kingdom.

THE COURT: You may inquire, Mr. Kobre.

Q. Good afternoon, Dr. Parrott.

A. Good afternoon.

Q. Dr. Parrot, can you just tell the Court just a bit about yourself, where you are from and just a bit about your personal background?

A. I am British, born in London, but now in Swansea in Wales, working at the University of Swansea for the past six years.

Before that I was at the University of East London.
Q. Let's start back a bit.
Where did you do your undergraduate studies?
A. That was at University of Durham in north of England.
Q. Did you receive any particular awards or honors at Durham?
A. I got a 2.i degree and I was one of the two highest students.
Q. Then did you pursue your doctoral studies?
A. Yes. I got a research studentship at the University of Leeds.
Q. What is a research studentship?
A. This was funded by the Medical Research Council and they give out a limited number of these studentships for people to study for a PhD.
Q. Among those at Durham, how many Medical Research Council studentships were given out?
A. Well, two students from Durham were given these. One was at London and one was at Leeds, and it was given by Leeds rather than by Durham.
Q. Just, again, where did you receive your doctorate from?
A. My doctorate was from the University of Leeds, yes.
Q. What is your current position?
A. I am a professor at Swansea University.
Q. Can you please summarize for the Court your current major areas of research?

A. Well, for the past 18 years, I have been studying Ecstasy, particularly in recreational users. Before that I studied cigarette smoking and a range of other drugs.
Q. Before you were a full professor at Swansea, where were you?
A. I was at East London, I joined there in the mid 1980s as a senior lecturer and promoted to reader and then professor.
Q. What did you study at the University of East London?
A. That again was drug use. I have been studying various types of drug use for many years now.
Q. Before that you were at the University of East London?
A. I was working for the Ministry of Defense in the U.K. in their Institute of Naval Medicine where we were looking at the effects of sea sickness drugs on naval personnel.
Q. And did that work involve work for the British government?
A. Yes. It was a British government funded study.
Q. You mentioned earlier you conducted research for approximately 18 years regarding Ecstasy or MDMA. Approximately how many papers have you published specifically regarding MDMA?
A. I think that's a matter of debate, but I think it is roundabout 50. I haven't counted it recently, I am afraid.
Q. Thank you.
A. I think it is 47 to be conservative, I guess.
Q. Were all of those published in peer review journals?

A. Those, yes.
Q. Can you describe a little bit more specifically the main areas of your research concerning MDMA?
A. I started various areas, particularly news and cognition, the effects on feeling states and then cognition, I published one of the first studies looking at memory in Ecstasy users, and we published several studies in that area.
Q. Can you give the Court some examples of some of the journals you published in?
A. Psychopharmacology, Drug and Alcohol Dependence, Human Psychopharmacology, European Journal of Psychopharmacology-- all of the major psychopharmacology journals.
Q. Have you received any awards relate to your MDMA research?
A. Yes. I received two awards. One was in 1999 by the British Association of Psychopharmacology. And I was given their annual journal prize.
Q. Was that with respect to a specific research paper?
A. Yes. That was the paper where we published results of one of the first studies to find memory deficits in young Ecstasy users compared with young age match controls.
Q. You mentioned you had received two such awards?
A. Yes. The same award was awarded to Helen Fox and myself as her supervisor in 2002.
Q. What was that? Was that also with regard to a specific search paper?

A. That was another Ecstasy research paper. Basically by that time we had published a number of papers looking at the memory deficits of Ecstasy users. We were also interested in why some Ecstasy users reported problems and others didn't. So we split the sample into two subgroups depending upon whether they reported problems or not. So half of the group were people who reported they had had problems with Ectasy and the other group reported they hadn't.

Q. When you said "problems," what kind of problems were you referring to specifically?

A. Well, the question is very simple. It said, have you developed any psychopharmacological problems as a result of taking Ecstasy.

Q. And the results?

A. Some said yes, they had. Others said no, they hadn't. We then gave everyone our usual battery of memory tests and what we found was that there was no differences between the two subgroups. Then when we split the group into dosage levels, we found significant defects related to dosage. So for heavy users who used over 100 times, reported the worst problems on two particular tests. That was spatial memory and the logical thinking test.

Q. Let's move on a bit, and then we will come back to this a little bit later.

A. The basic thing was that both groups reported that. So

even those who reported problems had that.
Q. Professor Parrot, are you on the editorial board of any journals?
A. Yes. Drug and Alcohol Dependence, Human Psychopharmacology, Journal of Psychopharmacology, and the other one I have forgotten. I think it was mentioned earlier, Current -- it used to be a web-based journal -- it is a fourth journal anyway.
Q. Are you an academic reviewer for any peer review journals?
A. Yes. Over the years, I have reviewed for a large number of journals. I think it is about 30 about now.
Q. Before we sort of get into the substance, can you give the Court a brief background regarding the physical makeup of the compound that is MDMA?
A. MDMA as is stimulant. It is methylenedioxymethamphetamine derivative, so it is similar to the parent compound which is a powerful stimulant drug, but interestingly, it has got what is called a ring substituted, methylenedioxymethamphetamine derivative, and that makes it somewhat different from methamphetamine. In particular, it affects serotonin rather than, preferentially, a dopamine.
Q. Before we discuss the current knowledge regarding the effect of MDMA upon humans, I want to ask you, Professor Parrott, how if at all the state of scientific knowledge regarding the effects of MDMA has changed since 2001?

A. Well, basically, the deficits reported in 2001 have been confirmed in subsequent research. In addition to that, we discovered a number of new areas of deficits which were not known during 2001.

Q. Have the studies that have been performed since 2001 controlled for what you have heard before discussed here as confounding factors?

A. Well, many of the studies before 2001 were interested in particularly polydrugs confounds. When I reread my paper published in 1998, I had written half a paragraph on the potential compound of cannabis as a potential confound to MDMA. And I discussed several papers which had been looking at that as a confound. So people were aware of polydrugs confounds before 2001.

Q. And there were papers that specifically controlled for those confounding factors?

A. Well, they talked about it. They debated it. In subsequent years, the studies are certainly becoming more sophisticated in their attempts to investigate this as a potential issue.

Q. Have any of the psychobiological deficits associated with MDMA that were known in 2001 been called into question by studies since that time?

A. No. All of the deficits reported in 2001 have been subsequently confirmed by later studies.

Q. Have there been recent studies with respect to the neurotoxic effects of MDMA?
A. One particularly good study is the Kish study which is probably one of the best today with the different factors and it has a very large sample size.
Q. If you could tell us a little bit about the methodology and the results that Kish found?
A. Well, they had two samples. One was 49. The other was 50. So they had known users of Ecstasy and Ecstasy users. And they put them through a standard sophisticated PET imaging neuroimaging test, and they found deficits in all regions of the cerebral cortex which as Val Curran described is the major part of the brain in humans. And the other area which was affected was the hippocampus.
Q. When you say "deficits," can you just explain a bit?
A. Well, they found reductions in the serotonin transporter density which had been described earlier. And then the cerebral cortex varied from minus 19 percent in some regions to, I think it was around about minus 40 percent in other regions. And they also found a deficit in the hippocampus, but I can't remember what percentage that was.
Q. What does it mean to say that there was a reduction in serotonin transporter?
A. As Val Curran described, this is the distal axon terminal. Basically, the Raphe nuclei which is the base of the brain, you

have serotonin neurons and they spend out very long thin axons to the distal parts of the brain. So these are thought to be very sensitive to damage. And then when you do these staining of the cerebral cortex, you find there is a reduction in the number of these serotonin transporters in the brains of the Ecstasy users.

Q. So what is the reduction in the serotonin transporters mean for the health of the axons?

A. Well, in functional terms, Kish also looked at memory performance in their users, and they found that the memory schools were impaired, so it was a functional aspect. I recall they also found a correlation between these measures.

Q. You mentioned before that Kish was one of the better studies. Can you just describe why you think Kish was a particularly good study?

A. Well, it is a very long paper to read. Brain is a very prestigious journal. It has to be an extremely good study to be published in there. And they looked at so many potential confounds in their subject selection and their analysis. For instance, they looked at the effects of other drugs. In particular, they looked at the potential confounds of methamphetamine, the parent compound. And they concluded that some of their users had used methamphet and others hadn't and they split. They found that the imaging deficits, serotonin deficits were present in both groups. So they concluded it

wasn't methamphetamine use that led to the serotonin deficits. It was the MDMA deficits.

Q. So what does the Kish study mean for the question of neurotoxicity, whether MDMA causes neurotoxicity?

A. It is very clear evidence that Ecstasy users are suffering from neurotoxicity in higher brain regions and the hippocampus which is responsible for memory.

Q. You mentioned that since 2001, some studies have been confirmed, some of the deficits have been confirmed, but you also mentioned that there have been some new areas of dysfunction that have been discovered. Can you tell us a little bit about those?

A. One area that was not recognized in 2000 is prospective memory, and the first reports were published in 2001. Prospective memory is remembering to do something in the future. So if you arranged to meet somebody at 5 o'clock for a drink and you forget to turn up, that is a failure of prospective memory. So prospective memory is very important for organized intellectual activity. The first reports of deficits published in 2001 and then subsequent group studies have confirmed this in a number of trials.

Q. Are there any other new areas of dysfunction that have been found since 2001?

A. Well, one area is in visual performance. There are two Australian groups who recently linked together who found some

subtle differences in visual illusions in Ecstasy users compared to controls, and they relate this to deficits in the occipital cortex which is the region in the back of the brain responsible for visual processing.

Q. Is there any particular reason why a deficit in the occipital cortex would be particularly relevant?

A. Well, it is important for vision. There is another study published in 2005 where again they reported visual deficits. So it is only two groups, so it is very new area, basically.

Q. You have heard described three or four sort of chronological time periods that have been studied with respect to MDMA, sort of an on drug period, then sort of followed within the next week and then sort of a chronic effect. So I would like to just walk through these three areas. If we could just start with the on drug effects. Could you briefly describe sort of on drug effects on humans?

A. It releases serotonin, so it is a very powerful stimulant. You have arousal, increase in blood pressure, heart rate, breathing rate. In mood terms, you can get very mood intensification. The predominant moods tend to be positive. You get feelings of euphoria. But you can also get negative feelings, for instance, an increase in anxiety and tension which, again, is not typical of many synapse stimulant drugs.

Q. What is serotonin syndrome?

A. Serotonin syndrome was first described in medications which

lead to increased serotonin. And you had occasional reports of persons suffering from serotonin syndrome which is due to too much serotonin. And in particular, some of the effects include overheating, confusion, also psychomotor aspects, repetitive psychomotor actions. And if you give serotonin symptom lists, there are reports of many users are probably experiencing a mild form of the serotonin syndrome and, occasionally, you get people more moderate and more severe aspects. And this is when they need hospitalization to reverse the hyperthermia.

Q. Can MDMA use cause death?

A. It does cause death, unfortunately, yes.

Q. Can you describe how that would happen?

A. The two main forms of acute death, one is hyperthermia. This is where people overheat and their bodies overheat and that can cause an acute hyperthermic or overheating reaction. There are some deaths which have been talked about.

The other cause of death is hyponatremia. And basically when MDMA is taken, it can heat up the body and, presumably, the brain as well, although that is a presumption. And you get this increase in hyperthermic activity. People feel hot. They also feel thirsty because they are feeling hot. They are sweating. Many Ecstasy users feel this hyperthermic response. So they drink water instead. And in addition, you get confusion so people often are confused about how much water they have drunk. So what can happen then, is they've got too

much water in their body fluids.

In addition, MDMA stimulates for release of what is called the antidiuretic hormone. I said that slowly. It is antidiuresis. So it is against weeing or peeing. So this means you wee less and you accumulate more fluids in your body. So coupled with that, you can have this dangerous acute reaction of hyponatremia.

Q. You referred before to some of the cognitive effects that MDMA can have in an on drug user. Have you personally performed any studies regarding those cognitive effects in an acute user?

A. Sorry. I missed that.

Q. You mentioned before that MDMA could have some cognitive effects in an on drug -- when a person is on MDMA. Have you personally done any such study?

A. Yes. We have tested recreational Ecstasy users at dance clubs and raves. In a 1998 paper we tested recreational Ecstasy users using what was then an Apple message pad which was then an early portable micro-computer I guess it was superseded by more modern devices, but in 1998, it was state of the art. It had a screen and we gave tests to people at the club. One of the tests was a visual scanning test and the other was a memory test. And what we found was, the Ecstasy users were impaired on the visual scanning tests while at the club and then compared with baseline and then they recovered

two days later. So it had an acute effect in impairing visual scanning. We gave interviews to people as well, and they reported they found it difficult to focus on the task.

THE COURT: Is this a convenient spot to suspend for the evening?

MR. KOBRE: Yes, it is, your Honor.

THE COURT: Dr. Parrot, I am going to ask you to step down, sir. You are excused. And we will resume tomorrow morning at 10 a.m.

Have a good evening, sir.

(Witness excused)

THE COURT: Are there any matters that counsel want to raise before we conclude for the evening?

Any issues from the government?

MR. CHUNG: Not from the government.

MR. RORTY: Not from the defense.

THE COURT: We have the completion of Dr. Parrot and one other witness?

MR. CHUNG: Yes. Dr. Hanson after Dr. Parrot.

THE COURT: There are no deadlines, but what is counsel's best estimate of when we might conclude the taking of evidence tomorrow?

MR. CHUNG: We estimate for Dr. Parrot another hour and a half of direct examination and, obviously, I don't know how long cross-examination is going to take. I can say that

for Professor Hanson, it will be equal length, about hour and a half to two hours of direct.

THE COURT: So we will definitely be working into the afternoon, if not through it tomorrow and I have got the day cleared. So we will work from 10 tomorrow morning.

MR. SPORN: Is this a good opportunity for me to request that the hearing be transcribed pursuant to CJA?

THE COURT: Yes. You will complete a voucher. I will sign it. You can get it straight away, because I am going to invite the parties to make a further submission to me based upon the transcript here. So you can request this on an expedited basis.

I will see you tomorrow at 10 a.m.

Have a good evening.

(Proceedings adjourned until 10 a.m., December 7, 2010)

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK
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UNITED STATES OF AMERICA

v. 09CR1136(WHP)

SEAN McCARTHY,
LARRY WARREN HOUGH,
Defendants.

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New York, NY
December 7, 2010
10:10 a.m.

Before:

HON. WILLIAM H. PAULEY III

District Judge

APPEARANCES

PREET BHARARA
United States Attorney for the
Southern District of New York
DANIEL CHUNG
ELISHA KOBRE
Assistant United States Attorneys

MICHAEL SPORN
SCOTT MICHELMAN
JAY RORTY
Attorneys for Defendant McCarthy

JOHN C. MERINGOLO
Attorney for Defendant Hough

(Hearing resumed)

THE COURT: Are there any preliminary matters that the parties wish to raise?

MR. RORTY: No, thank you.

MR. CHUNG: Not from the government.

THE COURT: I have one. Thinking about this last evening, this Court has granted the application of Mr. Michaelman and Mr. Rorty to appear pro hac vice in connection with this hearing on behalf of the defendant Mr. McCarthy.

Mr. McCarthy, I would like to hear from you that you consent to their serving as counsel, advocating on your behalf here during the course of this hearing. I note that you are joined by the counsel who the court has appointed for you, Mr. Sporn, but he is decidedly taking a backseat to the conduct of this hearing.

So my question to you, Mr. McCarthy, is do you consent to having Mr. Michaelman and Mr. Rorty represent you in connection with this hearing and the conduct of this hearing?

DEFENDANT McCARTHY: Yes, your Honor, I do.

THE COURT: Yes, Mr. Sporn.

MR. SPORN: Before you go to the next point, the Court should be aware that this was not a matter that was not discussed with Mr. McCarthy. He was on board with this from the beginning.

THE COURT: I am confident that it was. I also thought that I may have previously had this discussion with Mr. McCarthy in open court, but in looking at a prior transcript, it appears to me that I may not have. So I just want to make it clear here on the record.

MR. SPORN: Thank you.

THE COURT: In addition, for the sake of the record, Mr. Meringolo, does your client join in this application that Mr. McCarthy is making?

MR. MERINGOLO: Yes, he does, your Honor.

THE COURT: I take it that if at any point during the course of the hearing that you have any interest in asking a question of one of the witnesses, that you will alert me to that fact?

MR. MERINGOLO: Absolutely.

THE COURT: And that yesterday you had no questions that you wanted to pose to any of the witnesses?

MR. MERINGOLO: I did not.

THE COURT: Very well.

I think that we are ready then to resume then with Dr. Parrot.

Good morning, Doctor.

You may take a seat.

Do you understand, Dr. Parrot, that you continue to be sworn as a witness under oath in this proceeding now on trial?

THE WITNESS: I do.
THE COURT: Counsel, you may inquire.
MR. KOBRE: Thank you, your Honor.
ANDREW CHARLES PARROTT,
recalled as a witness by the government,
having been previously duly sworn, testified as follows:
DIRECT EXAMINATION (Continued)
BY MR. KOBRE:
Q. Dr. Parrott, have you had an opportunity to review a document dated May 2001 by the United States Sentencing Commission titled "Report to the Congress, MDMA Drug Offenses, Explanation of Recent Guidelines Amendments"?
A. Yes, I have read it.
Q. How did you come to review that document?
A. You sent me the document.
Q. Now, I am going to read you from a portion of the document titled "Health Hazards." Have you reviewed that portion of the document?
A. Yes, I have read that section.
Q. There is a statement in there that says the following. It says: "Finding from multiple scientific studies describing symptoms of acute toxicity from MDMA use, including mental status changes, hyperthermia and other symptoms associated with serotonin syndrome" -- I skipped a little portion of that. Let me just back up again.

"A comprehensive review of the scientific literature reports findings from multiple scientific studies describing symptoms of acute toxicity from MDMA use, including mental status changes, hyperthermia and other symptoms associated with serotonin syndrome."

Can you comment on that statement?

A. I would agree with that statement.

Q. Does that statement refer to some of the acute effects of MDMA that you talked about yesterday?

A. It certainly refers to some of the acute effects of MDMA and related to the serotonin syndrome, yes.

Q. I want to take you to another statement in that same section of the report. The statement says that the brain scan comparison of MDMA users with non-users indicated that users had a significantly reduced number of serotonin transporters throughout the brain and that the magnitude of the loss was associated with greater use of the drug. Do you agree with that statement?

A. Yes, I agree with that statement.

Q. Could you talk briefly -- and you may have done this a little bit yesterday -- but if you could just talk briefly about some of the scientific literature that supports that statement?

A. Well, there have been a number of brain imaging studies and they have been reviewed by Cowan in 2007. And Cowan concluded

that one of the most consistent findings of the imaging studies on Ecstasy users was a reduction in serotonin transporter density in the higher brain regions.
Q. What does that mean a reduction of serotonin brain transporter density?
A. Serotonin cell at the base of the brain stem, the Raphe nuclei, isn't damaged, the cell remains alive. However, it sends very fine axon terminals to the higher brain regions. And these are measured by PET scans and other imaging devices in terms of the distal axon terminals. And the model is that these are lost, these are damaged to a certain extent in Ecstasy users and that you get a reduction of these in the higher brain regions. That's also what Cowan concluded.
Q. Was Cowan a review paper?
A. Cowan was a review paper, yes.
Q. Can you tell us about some particular individual studies that found the phenomena that you are referring to, the damage to the axon?
A. Well, Cowan reviewed many studies until 2007 and found a fairly consistent finding. But more recently, Kish -- which we mentioned briefly yesterday -- has confirmed this again in probably one of the best controlled studies that has been published so far. It is very large study, and they have controlled for many potential confounds. As they describe in the paper, they tried to control for every confound they could

look at and still found deficits.
Q. Was Kish a study involving human subjects?
A. Yes. It was human subjects, and I think it was two sample sizes, 49 and 50. One was a control, non-users, and the other was Ecstasy polydrug users.
Q. In the Kish study, what sort of dosages were the subjects taking? What sort of dosages of MDMA had the subjects in Kish taken?
A. Well, the Kish paper in its introduction said it aimed to test an average user of Ecstasy. And the average number of tablets was around about 200, but there was a range.
Q. When you say 200, do you mean the lifetime episodes of use?
A. I would have to check the paper. I know I have a figure of 200. I am not quire sure if these tablets were lifetime episodes, I would have to check the paper for that. That is my recollection, anyway.
Q. Was the Kish paper referring to subjects whose use of MDMA you would say was fairly typical?
A. The Kish paper, in its introduction, aims to get, as they say, an average user, so it was a range of user, but that was their intention.
Q. Are there any particular prior neuroimaging studies similar to Kish that you can tell us about?
A. Well, the Reneman group has undertaken studies, Sentel, McCann -- they have all published studies. It is really not my

area of expertise, but I have read the papers. And there seems to be a fairly consistent finding that there is a reduction in density of these serotonin transporters in many of these studies.

Q. Thank you, Professor Parrott.

I am going to read you another statement from the Sentencing Commission report that I referred to earlier, and I am going to ask you to comment on it.

THE COURT: If you would just tell me what page you are reading.

MR. KOBRE: Yes, your Honor. I am referring to page 9, right now, the last paragraph on it.

THE COURT: Thank you.

BY MR. KOBRE:

Q. In the third sentence of that paragraph, it says that users demonstrated significant impairments in visual and verbal memory.

A. Sorry. What paper was this, again?

Q. I am referring now to the Sentencing Commission report?

A. Sentencing Commission, sorry.

Q. Sure. It says that users demonstrated significant impairment in visual and verbal memory. I want to ask you first about verbal memory.

Can you tell the Court about some studies and what has been found with regard to MDMA use and its effect on verbal

memory?
A. Well, a number of studies have investigated verbal memory and many of them have found deficits in Ecstasy users, so it is a fairly consistent finding across many studies -- not all.
Q. Before maybe we turn to some of those studies, can you define what is verbal memory?
A. Well, a typical verbal memory task would be to give somebody what is called a super span task, that is a span of words longer than you can normally memorize, typically, 15 or 16 words. So an average person might well recall 10 or so, and then and you see if the Ecstasy user can also remember that number or remembers more or less.
Q. Can you describe some of the research regarding verbal memory and the effect of MDMA on verbal memory?
A. Well, one of the most widely used tests is the Rey Auditory Verbal Learning Test, RAVLT, and this consists of giving the reader a list of 16 words and then asking them to recall them. Then the list is given again and they are given a second recall. Then given a third time and again, often to five times, and you measure how many words they recall. And, typically, you get a slight increase with each repetition of list.
Q. There was some talk yesterday about a paper by Rogers. Can you describe whether Rogers investigated the effect of MDMA on verbal memory?

A. Sorry. Is this for Rogers review?
Q. That's the paper --
A. The meta-analysis?
Q. Yes. I think that's the paper that Dr. Curran referred.
A. Yes. There are two Rogers. There is a Rogers et al. meta-analysis. So the Rogers et al. meta-analysis was published in 2009 and they looked at many different studies which had used the Rey Auditory Verbal Learning Tests. And I think they found there were about nine studies. There was quite a difference in findings across studies.

A couple of the studies found no indication of performance impairment in the Ecstasy users, indeed, slightly better performance -- it wasn't significant -- in the Ecstasy users compared with controls. One of the studies, I think, though, performance was very similar. And the other studies spoked relative decrements and several of these studies showed significant decrements.

Rogers et al. then undertook a meta-analysis which was described by Val Curran yesterday which is basically reducing all of the studies to a simple common denominator and then seeing what is the average effect. When they did this, they concluded that over all these different studies, there was a significant decrement in the Ecstasy users compared with controls.

Q. Does that mean that there was a decrease in the number of

words that the MDMA users were able to recall?
A. Yes. They recalled less words.
Q. We heard testimony yesterday from Dr. Curran that the decrease in some of the studies, the number of words that were decreased, that it was relatively a mild effect. Could you comment on that?
A. Again, there was tremendous variation between studies. Some studies found small deficits. Others found larger deficits. So there was variation.
Q. Could you describe a study that has found a large deficit, what you would consider a large deficit?
A. Well, I can't recall which of the Rey papers found a large deficit. As I say some of the studies found larger deficits. I cannot remember which ones found the larger deficits.
Q. Are there any papers outside of the Rogers review that also studied verbal memory and its effect on MDMA?
A. There is a very good paper by Gouzoulis-Mayfrank published in the year 2000 that is in the Journal of Neurology, Neurosurgery and Psychiatry, I believe. They did a very well controlled study in that they had 28 Ecstasy users. And we have heard already, Ecstasy users are often polydrug users. And round about 24 or 25 of these also used cannabis. So they then generated a matched control group of cannabis users where they tried to match the use of cannabis across all participants. So the cannabis user group actually had four or

five people who had never taken cannabis, simply is they matched as closely as possible the Ecstasy users. And then they had a third group who were the clean group, the control group who had never taken either cannabis or Ecstasy.

And they give them a German version of the Rey Auditory Verbal Learning Test which is slightly different. It only has 15 words and, obviously, German words, so it was not included in Rogers meta-analysis. They found significant deficits in the Ecstasy users compared with the cannabis users. And, also, they found that the cannabis users were not impaired compared with the control group. So this was really quite a nice benchmark study for showing basically the effects of Ecstasy rather than cannabis.

Q. Are there any studies -- I am looking at verbal memory in Ecstasy users after a period of abstinence?

A. Yes. Morgan looked at verbal memory. This wasn't the Rey Auditory Verbal Learning Test he used. This was a Rivermead paragraph and, basically, the Rivermead task is where you are given a short paragraph with round about 21 pieces of information. And then you are asked to recall that, write the story back down again. And then it is scored in a standard format for how many items of information you recall.

In the Rivermead paragraph recall test, Morgan, in that paper in 2002 -- this was published in the Journal of Psychopharmacology, they had four groups. They had the control

users. They had a polydrug user control group. They then had a current Ectasy user group. And they had a former Ecstasy user group who had stopped using Ecstasy for at least six months on an average -- the average quit time was two years.

And my recollection of the paragraph recall test was that the controls recalled about 8.9 items; the polydrug about 7.5; the current Ecstasy, I think, was round about 6; and the former Ecstasy users, round about 4.5 items of information. So in fact their recollection of information was really quite a lot higher.

Q. To summarize, if you compare the non-user control group with the former Ecstasy user group, they were able to get about half --

A. Probably 55 percent, 60 percent, something like that, yeah.

Q. And these were users who have been abstinent for how long?

A. I would say the criterion was six months, and the group mean was two years.

Q. So what does that imply to you about whether the effect of MDMA has some permanency?

A. Well, certainly that group seemed to show quite an enduring deficit in their memory.

Q. You described just a moment ago, what you called the Rivermead behavioral test?

A. Rivermead, yes.

Q. Did Rogers also perform a meta-analysis with respect to

that test of verbal memory?
A. Yes. Rogers does have a review 2009, and it was a similar number of studies. I can't recall how many exactly, but it was round about seven, eight, nine studies used for Rivermead. Again, it was the meta-analysis and, again, they found a variation in findings. Some studies didn't find a deficit and others did.

In matters of meta-analysis, they did it on two groups. One was the current users. And there the meta-analysis, they didn't find significant effect. There was lower performance in the Ecstasy users, but it didn't reach significance.

They then did a separate analysis on the four studies which had looked at former users. And that included the Morgan study -- that was one study, three others were included as well. In their meta-analysis, they showed that all four studies showed significant impairments in the former users and that the overall effect was significant.

Q. So what do all of these results sort of lead you to conclude with regard to the effect of Ecstasy on verbal memory?
A. Certainly in term of the Rivermead test, it indicates the memory effects are enduring.
Q. Professor Parrott, we have spoken about verbal memory. Can you tell the Court what is prospective memory?
A. Prospective memory is remembering something in the future.

It is a more complex form of memory in that if you arrange to meet somebody at 5 o'clock on the evening -- I think I briefly described it yesterday evening. If you are meeting somebody at 5 o'clock and you forget to turn up, then that is a failure of prospective memory.

Prospective memory is more complicated because it involves both planning, so it is thought to involve frontal aspects like remembering that at 5 o'clock you have to meet somebody and then a memory component that you have to remember what it is you have to do, that you have to meet such and such in a particular place. And prospective memory has been studied in Ecstasy users.

Q. Is there a consensus of scientific opinion regarding how repeated use of MDMA affects a human's prospective memory?

A. There are several studies which have looked at this and they have generally found deficits in prospective memory. The first studies were by Heffernan et al. in 2001, and then a study by Rendell 2007.

Q. Just to be clear, these studies that we are talking about now, we are not talking about acute studies. Are we talking about after the person is no longer on the drug?

A. Typically, they will have a one-week washout. That's a typical description for many of these studies. That would be an average for most of the research in this area. Some have a shorter period, some have a longer.

THE COURT: I don't understand that term. Can you explain to me what you meant when you say a one-week washout?

THE WITNESS: If you took Ecstasy on a Saturday, then seven days later you could then be tested. And the theory is that you no longer have the drug in your system but, also, that you will no longer be suffering the withdrawal effects that we talked about yesterday, the mid week blues, the low levels of serotonin.

THE COURT: How long does Ecstasy remain in someone's system where it would be detectable?

THE WITNESS: That is a complicated question because it is metabolized into other drugs such as MDMA, but it is generally quite a rapidly acting drug. It is fairly quite rapidly metabolized, so it has peak effects for three, four hours, and then the effects start to wear off and you will have reducing amount of drug in your system.

The tail of any drug metabolism is very long, so you have a peak and long tail, so you may well have small amounts of drug in your system for quite a period. But in terms of peak effects, that is thought to be fairly short for Ecstasy. However, one crucial factor is that, as Val Curran noted yesterday, you have problems days afterwards because your tryptophan hydroxylase takes time to recover. So it takes a while for your serotonin system to recover after taking the drug. That's why you need a washout period to try to make sure

that you are not testing the recovery effects of the drug.
THE COURT: Thank you.
BY MR. KOBRE:
Q. In terms of prospective memory, I think your testimony was that it is affected by MDMA, and you were starting to tell us about some of the studies. Before we get there, which part of the brain would generally be implicated in prospective memory?
A. The two parts of the brain are generally thought to be the hippocampus which is very important to memory and also the frontal lobes which are important for planning. And so it is thought that prospective memory is particularly involved in both functions.
Q. Can you tell us some of the research that has been done regarding the effect of MDMA on prospective memory?
A. Well, Rendell has probably taken the most comprehensive study. That was published in Psychopharmacology in 2007. Rendell et al. And they had a virtual game board task.
Basically, Rendell is not really psychopharmacology. He comes from a prospective memory background, so he is more of a cognitive psychologist. And he developed this game board which consists of throwing dice and going round the board five times to represent five days. And as you go around the board, you have to remember to do certain things and respond to certain cues. So you have a cue on the board which you will pass. As you pass that cue, you know that you have to do

something. So the question is, do you remember to do that thing when you pass the cue. So the board doesn't tell you what to do; it just gives you the cue for doing that action. So it may well be that you pass cues and fail to do the task. So that's a failure of prospective memory.

They had three groups. They had non-user controls. They had what they call light intermittent Ecstasy users. And these were people that typically used once a month or less, so it is not very frequent users. And they had a second group who typically use twice a month or more, so they were seen as more the moderate to heavy to regular users.

One of the benefits of this task is they generated lots of prospective memory scores, which means it was a very sensitive test. When they analyzed the data, they found that the low intermittent Ecstasy group was significantly impaired compared with the non-user controls. And then when they looked at heavy Ecstasy users, they were significantly impaired when compared to the controls and to the intermittent group. So they had very nice dose-related data.

Q. Just to clarify, these were effects were observed off drugs, after a period of some days?

A. In this particular study, because Rendell was not a psychopharmacologist, their particular criterion for abstinence wasn't a good one. I think they said they had to be drug free for either one day or two days. I can't remember. And they

didn't differentiate between drugs. Many studies say you have to be free of alcohol for one day or cannabis for two days, but free of Ecstasy for seven days.

This particular study, because they were not particularly sophisticated psychopharmacologists, they had not done that. So that is a potential criticism of the study, however, if you look at the user pattern of the Ecstasy users, if they are using once a month or less, it is unlikely that they would have taken the drug in the days afterwards.

Q. I think you described some other research also regarding prospective memory, other studies that were done?

A. There have been other studies Heffernan et al. has tested this. And they found it both on questionnaires, so if you asked Ecstasy users do you suffer from memory problems, what you tend to find is a significant increase in reports of prospective memory deficits in the Ecstasy uses. Heffernan et al. also used a video game. And in that study they also reported deficits.

Q. Do the finding you referred to in Rendell and Heffernan, what do those sort of findings imply for functioning in every day life?

A. Well, to give you one practical example, I actually supervise lots of students doing projects. And many years ago when we first started out, my research student said to me, we are having problems. The controls are turning up for the

appointments and the Ecstasy users keep on missing appointments.

I said, well, it is just because they lead chaotic lifestyles or something like that. And I didn't think much more about that. But then when the Heffernan papers came through, first reporting prospective memory deficits in Ecstasy users, the penny dropped, and I suddenly realized why the Ecstasy users in particular were missing their appointments.

So now when I supervise my project students, I get them to phone up, I get them to a mobile phone number and I say to them, phone them up before the test to make sure that they are going to turn up to save wasting time.

Q. Thank you.

What is executive functioning?

A. Executive functioning is thought to be one of the highest aspects of human activity. It is planning, it is strategic. It is problem solving -- all of these higher functions.

Q. Is there a consensus of scientific opinion regarding how repeated use of MDMA affects an individual's executive functioning ability?

A. Yes. There have been a number of studies conducted in this area, and this is now thought to be the other area, in addition to memory, where Ecstasy users often report impairments.

Q. Can you describe some of the research regarding executive functioning?

A. Well, one of the first studies was undertaken by Michelle Wareing in the British Journal Psychology published in 2000. And she found a significant deficit in a task which is a strange task to describe. It sounds very simple, but it is actually quite sensitive. And it is called random letter generation. So you are asked every few seconds to generate a letter. And then on a regular period you generate another letter. And you are not supposed to repeat letters or do it in strings or have consecutive letters. And it is actually quite difficult. Many people can do it at a rate of one letter every four seconds, but the fun starts when you start giving the task more rapidly, the two seconds and one second. Wareing did this in their study, and they found that the Ecstasy users were impaired and some of them found difficulty with the task.

Q. Just to clarify, again, we are talking about an off drug observation?

A. These were Ecstasy users off of drugs, yes.

Q. Have those findings of Wareing regarding executive functioning, have they been confirmed in later studies?

A. Well, various executive functions -- do you want me to talk about another type of executive function?

Q. If they relate to a later study -- later after Wareing, I believe you mentioned was in 2000?

A. Right, yes. My recollection of Rogers review is this is one of the areas they looked at. And, again, my recollection

is they did find executive frontal problems were significantly impaired over a range of studies. Again, there is variation in findings but, on average, they found a deficit.

Q. I think you mentioned before that executive functioning is somehow related to logical reasoning?

A. That is right.

Q. Can you describe some of the research about how MDMA affects a user's ability to engage in logical reasoning?

A. Well, Fisk et al. published a paper in 2004 that is in the Journal of Psychopharmacology, and they looked to Ecstasy users versus controls. And they gave what is called an Aristotelian syllogism test. It is along the lines of if A -- some of A are B and some of B are C, are all A, B or all A, C -- sorry, it is not very accurate, but it is along those lines and you have a series of these problems.

Now, on this particular study, they trained all of the participants on this logical problem solving beforehand and then they gave them on the basic problem solving, and then they gave them tests to see how good they were at this particular problem solving procedure. And they found a significant deficit in the Ecstasy users.

One problem was, the deficits in this particular study were not just related to MDMA; they were related to other drugs as well, so they couldn't offer firm conclusion about the role of other drugs, although when they analyzed it, they said that

the strongest relationship was with Ecstasy.
Q. Did they analyze the data using statistical methods?
A. Yes.
Q. Were they able to sort of using statistical methods control for use of other drugs?
A. As I said, what they found in this particular study was this particular logical reasoning was associated not only with Ecstasy but other drugs such as cocaine and amphetamine.
Q. Professor Parrott, so far we have talked about verbal memory, prospective memory, executive functioning, logical reasoning. There is one sort of area further in this section that I would like to cover which is social intelligence, and if you could tell the Court what that is?
A. There is a paper by Rey et al. that is published in Journal of Psychopharmacology in 2006 and they tested both executive functions in Ecstasy users, and they gave what is called a social intelligence questionnaire, which is a questionnaire developed by other researchers. And it looks at subtle processes which underlie social interactions such as, do you find it easy to understand other people's emotions -- that sort of quotation is the sort of question covered in that questionnaire.
What they found was that the Ecstasy users reported deficits in that questionnaire. And when they controlled for other drug use, they found that the deficits remained after

controlling for these other drugs.
Q. So was it their conclusion that the deficits were related to Ecstasy?
A. In their theoretical discussion, they hypothesized that it may well be an aspect of this higher planning, higher executive processing that was the hypothetical explanation for their finding.
Q. Just returning now to the Sentencing Commission report on page 9, and the statement of the report that Ecstasy users demonstrated significant impairments in visual and verbal memory, do these findings that you have talked about until now, do they speak to that statement?
A. Yes. In recent studies there have been a number of studies which have confirmed these sorts of memory deficits.
Q. I want to read you another statement from the Sentencing Commission report. And now I am referring again on page 9 to the last line on that page and it talks about a conclusion among reports that MDMA use may impair a subsystem termed working memory. Could you comment on that statement?
A. Well, again, working memory was what I talked about with Michelle Wareing related to executive functioning, and so working memory does seem to be impaired.
Q. And then referring to the top line on page 10 of the Sentencing Commission report: "It talks about the fact that these deficits in working memory, this form of disturbance it

calls it, is likely related to the well recognized neurotoxic potential of Ecstasy." Do you agree with that statement?
A. I'm sorry. Could you read that again?
Q. I will read you the entire statement which is: "It talks about a conclusion among some groups that MDMA may impair a subsystem termed working memory and that this form of disturbance is likely related to the well recognized neurotoxic potential of Ecstasy." Could you comment on that?
A. Certainly memory is associated with deficits -- the Kish et al. study showed that there was an association between the serotonin transporter loss and then memory impairments. I am not sure that the Kish et al. had a working memory study in their report. I will have to check on that. But certainly many groups found working memory deficits and verbal memory deficits. Certainly many groups have talked about it in theoretical terms as reflecting this memory loss.
Q. Is MDMA addictive?
A. It is generally perceived as non-addictive in certain light initial users it displayed very minimal addictive properties, so it is probably one of the least addictive drugs, however, if you look at heavy users, they start to display many of the classic signs of drug addiction or drug dependence.
Q. Can you describe some of the studies that have been done with regard to dependence on MDMA.
A. Well, Topp et al. published an Australian government in

19987 where they concluded that there was a syndrome of Ecstasy dependence, but it was untypical of other drugs. So, again, it was only showed in a minority of users.

And this was developed in later reports by Bruno et al. published in the Journal of Neuropsychology in 2008. They interviewed or surveyed -- I can't remember if it is a questionnaire or an interview -- about 1,500 people and they found 20 percent of the sample reported a symptom severity dependence scale score of 4 or more which they took to indicate MDMA dependence.

They then split the sample into two subgroups, the 80 percent who didn't report symptoms of this criterion and 20 percent who did. And they found that the dependence was associated with greater lifetime use and greater intensity of use. So, for instance, were people taking the drug more than once a week, and if they were, that was associated with dependence.

Q. So in looking at those studies is there a significant --

A. If I can correct that, the actual score on questionnaire was in the past six months have you taken Ecstasy more than once a week. So those people that tick yes to that were more highly proportioned in the dependence group.

Q. In looking at those studies, is dependence a significant issue in MDMA?

A. Once people move up the usage scale, then they start to

develop more of the classic signs of dependence.

One of the reasons Ecstasy is far less dependent producing than other drugs is its long time scale. With drugs like cocaine, you can take cocaine quite frequently and have effective hits. And this is less so than MDMA where you need this washout period to take it again.

So there is a study by Hopper et al. published in 2006. I cannot remember the journal, but it was one of the standard peer review journals, and they looked at symptoms of craving for Ecstasy. And they gave people a little microcomputer to keep on them. And this computer beeped at certain times and they had to report whether they were craving for Ecstasy.

And what this group found was minimal craving throughout most of the study. So when people beeped most of the time, they had no Ecstasy craving, however, what they found was, craving started to develop on the afternoon of the evening when they are planning to take the drug. And the craving then built up in the few hours before intended use.

So it is a very unusual drug, but it does have some aspects of dependency, but it is very unlike the classic drugs.

Q. But there are users who experience dependency on the drug?

A. Once people become very heavy users, they can display quite marked dependency and very repeated use.

Q. Is there data on the percentage of people who become

heavier users?
A. To that level of extreme dependence, I think it is probably quite unusual. I don't know of any percentage figures.
Q. Professor Parrott, I want to read you another statement from the Sentencing Commission report.
I am now referring to page 10, the first full paragraph and it states: "That another point of controversy surrounding the MDMA research literature is whether a loss of the serotonin sites and the corresponding impairment is permanent."
I want you, if you can, to comment on the question of whether the functional aspects -- that we have been discussing earlier, the impairments to memory -- whether there is any research discussing whether those are permanent?
A. Well, this is still very much a wide open question, but the Morgan study I quoted earlier is one of the very few studies which has looked at this. And certainly they have data on the former users that suggest that their memory impairments were enduring, but that obviously needs to be developed in further studies.
There is another by paper by Zakzanis published in 2006. I can't remember the journal offhand but, again, it is very small study and they were following up Ecstasy users over time. And what they found was that those Ecstasy users who carried on using tended to continue to develop memory problems,

whereas those that quit, they either remained or the memory performance improved.

So there's variation in findings. It is really far, far too early. We haven't got the adequate data to answer that question.

(Continued on next page)

BY MR. KOBRE:
Q. Would it be fair to say that there is data in both directions?
A. Yes, Morgan would be in one direction; Zakzanis would indicate some recovery, yes.
Q. Did Zakzanis indicate whether the recovery actually brought the users back to baseline?
A. My recollection of the scores was the scores often moved towards the baseline. I don't seem to recall that they reached the score they had earlier. I would have to check the paper.
Q. Mr. Parrott, have there been any studies regarding the chronic effects of MDMA upon the human immune system?
A. This is an area of interest. The animal literature shows that MDMA is a very powerful suppressant on the immune system. Connors in 2004 published a review in this area. Most of the review was focused on the animal literature. It showed that MDMA didn't reduce the immune system. They then quoted some studies. In the Connors review they looked at some studies by an Italian group Pacifici et al. they published a series of studies looking at immuno reactions in Ecstasy users. They found impairments on some of these measures.
Q. What sort of impairments, what were they looking at?
A. They took blood samples, like lymphocytes, white blood cells, natural killer cells. These were important for fighting natural killer cells, I suppose an accurate name. Their job is

to attack and kill foreign substances. You also got neutrophils which they also investigated. They found that there was a reduction in these natural killer cells in Ecstasy users.

Q. Were those studies performed while the subjects were on MDMA?

A. These were prospective studies followed over time. I can't recall if they are absent users or former users. The blood samples were taken off-drug.

Q. Off-drug?

A. Yes, off-drug. They also cited our paper which is perhaps the only humans paper on this where we asked users, have you suffered coughs and colds. What we found was a dose-related instance. This a study we published in 2002 in human psychopharmacology. This is an Internet survey of several hundred Ecstasy users. The heavier Ecstasy user group reported significantly more instance of this problem then the novice users with the modest group, intermediate. I think it was 35 percent of the heavy group reported this problem, but that was just self-reports.

Q. Can you tell the court what is cortisol?

A. Cortisol is an important neurohormone.

Q. Have there been any studies, we talked about the effects of MDMA on serotonin, have there been any studies regarding the effects of MDMA on human cortisol levels?

A. Basically if you administer an acute dose of MDMA in the laboratory, you will get an increase in many hormones for a few hours. Cortisol is one of those. Daumann and Verkes published a review in 2006 and they reviewed 12 studies which looked at the effects of acute doses of MDMA upon cortisol. They showed that in 11 of those studies you got an increase in cortisol. The 12th study didn't find an increase but that was of a low dose of MDMA.

So, in laboratory it certainly induces a consistent increase in cortisol. We have done two studies where we looked at cortisol in recreational users. These were users who went clubbing on Ecstasy one weekend; on the other weekend, they agreed to go clubbing to the same club with the same friends, same group of friends, same club, same day, but not take Ecstasy. We published that study in 2008 in the Journal of Neuropsychobiology. Interesting, the range of variables, and one of the most surprising findings we found was this increase in cortisol which was 800 percent. I talked to neurohormone people and they said this increase in cortisol is really quite a dramatic increase.

Q. You said 800 percent?

A. 800 percent.

Q. Describe what sort of long-term health effects can result from an increase of cortisol to that degree?

A. Cortisol is known to be involved in many functions,

cognitive. Basically cortisol, if I can digress slightly, is important for homeostasis. Homeostasis is our normal bodily control. In the normal body we have a cortisol, an endogenous cortisol rhythm.

So a few hours before we wake our cortisol system kicks into action and we start about 5, 6 in the morning to have an increase in cortisol. So by the time we wake at 7:00, the cortisol system is already getting us ready for action. It peaks after one or two hours, then it tails off and remains stable for the rest of the day. So cortisol is important for getting us up, getting us awake, getting us alert in the morning, then it remains stable over time. So that's endogenous rhythm.

The other side of cortisol is what's called reactive homeostasis. This is when we have stressors to the bodily systems which we have to face. If we face a stressful situation like walking down a dark alley and you are afraid or the dust bin is knocked over and you have this fear reaction, then your cortisol reaction will kick into gear. It also occurs during marathon running, endurance sports, high temperature. It's thought to be a bodily reaction to coping with stress.

Q. Repeated stresses of this nature, what kind of long-term health effects if any could there be?

A. When cortisol is released from your body, it stimulates

what's called a symphoneumatic action, so this is activity in the symphosympathetic nervous system which is the autonomic nervous system responsible for being active and alert. It's thought that we need a balance between sympathetic activity and parasympathetic activity because parasympathetic activity is the opposite and that needs bodily repair. We repair muscles during relaxation. When we are in the couch potato mode, our body is repairing itself. When we are in the sympathetic mode, then the body is being stressed.

One of the theories of cortisol is it's involved in stress. Hans Sile first wrote about this in 1951. Stress is essentially a physical reaction. It's where the body is having to cope with demands about above the normal. So the theory is if we are having lots of stress, that's bad for us in the long-term. So the theory is that MDMA is inducing in regular Ecstasy users regular periods of bodily stress and these may well be related to the long-term effects of the drug.

If I can add to that, Connors in his review said that MDMA can be regarded as a chemical stressor upon the immune system. That's a direct quote from his 2004 review.

Q. You mentioned that with respect to some of the cognitive studies there was some variation in findings. Can you tell the court, since 2001 have there been any studies or reviews done to explain these variations in findings?

A. I missed that question.

Q. When you were talking earlier about some of the cognitive effects of MDMA, you mentioned there was some variation in findings, some papers had variation in findings. Have there been any studies since 2001 to explain these variations in findings?
A. In 2006 I published a review paper because I was particularly interested in the variation findings, so in that review paper --
Q. Is that one of the six papers --
A. Yes.
Q. -- that were submitted to the court?
A. Yes. I was particularly interested in why there was such a variation in findings, as other people have testified in some studies you don't get deficits, in other studies you do. In this review I attempted to look at the factors trying to explain this. I found several factors.
Q. Tell us what some of the factors were?
A. One important factor was acute dosage, so those that have a large acute dose tend to have more problems in days afterwards than a lower initial dose. So acute dosage is one factor. A second very crucial factor is cumulative, a lifetime dose. Many studies who test quite light Ecstasy users don't find deficits; those who test heavy users do find deficits.
Another is the function being assessed. In terms of cognition, we know that certain aspects of cognition are

adversely affected, particularly memory, frontal planning tasks. Other aspects like system tension tasks tend not to be impaired. Another crucial factor is polydrug use. This has been an enduring question in the literature for many years now. Since before 2001 people were talking about the effects of cannabis and also other stimulants.

So in that paper, I looked at this in detail. I showed that in some studies of Ecstasy and cannabis users, cannabis was the main drug responsible for the deficits. Then in another group of studies of cannabis and Ecstasy users, Ecstasy was associated with the deficits but not cannabis. Then in another bunch of studies, because there were probably 30, 40 of these studies, it was both drugs.

Q. How do you reconcile those studies?

A. I looked at the studies and tried to tease out what factors were there. One of the key factors was probably the relative use of each drug.

Q. What do you mean by that?

A. How much, if you were a heavy user of both drugs, a light user of one drug and a heavy user of the other drug. For example, Croft et al., they published the first study in 2001 shock that in Ecstasy cannabis users, the deficits were related to cannabis and not Ecstasy. Their users of cannabis were 10,000 times lifetime, whereas the use of Ecstasy was 40.

Croft et al. published another study in the same year,

2001, I think it was on a psychophysiological measure. There the Ecstasy users used an average 283 times, although I stand corrected on that, the use of Ecstasy, use of cannabis was I recall I think 2.2 joints a week, again I stand corrected. Anyway it was light use of cannabis versus a lot heavier use of Ecstasy. In that study, they found the deficits related to Ecstasy rather than cannabis.

Q. Just to sum up, there are several factors that can explain the variation in the studies and one of them is, with respect to polydrug use, the relative use of the various drugs?

A. That's right. I also looked at the co-effects of stimulants and there are a number of potential confounds, and again, I found a variation in findings. In some studies they were important confounds. I think I mentioned the Fisk study in physiological reasoning. There the other stimulant drugs were crucial confounds. In other reports, they looked at this and found they were not confounds.

If I can cite one of those studies, Fox et al., 2002. She was my research student. She did a study where she matched the Ecstasy users and cannabis users, sorry, she had Ecstasy users who were also cannabis users. The control group was quite nicely matched on cannabis use. She found deficits related to the Ecstasy, so she controlled for cannabis in the design. She then also looked at the co-effects of other drugs such as amphetamine and cocaine because the Ecstasy users were

using those drugs. She showed that the deficits remained after controlling for those potential confounds.
Q. After looking at all these factors what does your 2006 paper tell us about MDMA and how it affects?
A. The main conclusion is it was complex. Do you want me to elaborate?
Q. Briefly.
A. In study after study, MDMA has been shown to be associated with various tremendous variation in findings. Some studies shows co-influence of other drugs because all these drugs are powerful.
Q. Are you familiar with the study by David Nutt in 2010 titled Drug Harms In the U.K, a Multi Criteria Decision Analysis?
A. Yes.
Q. Do you agree with the result of that paper?
A. No.
Q. Why not? First talk about methodology.
A. Can I talk about it in relation to his 2007 paper as well or not, just 2010.
Q. Start with 2010.
A. David Nutt concludes that alcohol is the most damaging drug. I agree. In my 2004 textbook, Understanding Drugs and Behavior, in the chapter on alcohol, I say that alcohol is the most damaging drug known to mankind. So if we are taking the

amount of damage caused to humans by drugs, alcohol is definitely number 1. But what Nutt seems to be confusing in this paper is overall damage to society and relative damage by a drug. So, I read in a newspaper article by Nutt, who was asked to comment about this review, he said even if only 10 percent of alcohol drinkers have problems, that's still an enormous cost to society.

So Nutt seems to be suggesting that 90 percent of alcohol use can be OK without causing particular problems. So only 10 percent of alcohol users are suffering problems. So, in his paper, he doesn't seem to be talking about effects of drugs; he seems to be talking about the effects to society. There I agree alcohol is high. But he then talks about drugs and their relative harm. He says alcohol is therefore one of the most harmful drugs. It's not. It's actually one of the safest drugs. If you look around this room, I guess most of us are probably regular alcohol drinkers. I guess most of us have been drinking alcohol 30, 40 years. We can probably drink alcohol for another 20, 30 years. Most of us in this room won't be adversely affected; 10 percent may well be. But it's relatively a benign and social drug.

Q. Can the same be said for MDMA?

A. Certainly not. Nor for cocaine, nor for cannabis, nor for methadrone. He puts methadrone down as low. He puts CAT, which is cathinone, down as a drug of low harm. He has

confused overall harm for society versus the actual specific effects of a particular drug.

Q. Does Nutt make any claims about MDMA that you wish to comment on?

A. In his 2007 paper, he compared MDMA with various other drugs. He said that MDMA was the 18th drug on the list of harm for 20 drugs in all. To reach that conclusion, he rated every drug on 9 harm scales. To take one example of those scales, one was a relative pleasure scale. So every scale was given a score from zero to 3.0. Nutt gave heroin a maximum pleasure score of 3.0. He gave smoking a cigarette a pleasure score of 1.9 I seem to recall. And the pleasure score for MDMA, I think was 1.6. But again these figures may be wrong.

Certainly, Nutt gave a lower pleasure score for MDMA than smoking a cigarette which to my mind is amazing, but it was important, in that the high score, on the pleasure score, Nutt recognized that the most pleasurable drugs, like cocaine, heroin, methamphetamine, are most damaging. So a high score in pleasure was taken to add to the overall harm score. He seemed to have artificially given MDMA a very surprisingly low pleasure score which contributes to its low harm potential.

Another question he asked about was injection potential. Again he said opiates and cocaine 3.0. MDMA, he gave a score of zero. Yet there are two or three papers documenting MDMA injections in Ecstasy users. So MDMA should

have had a higher score from zero. But again, it contributed to the artificially low score.
Q. The 2010 paper by Nutt, do you agree with that paper?
A. No.
Q. Are you familiar with the summaries of testimony that were provided for the defense?
A. I have read those, yes.
Q. I will read some statements from those summaries of testimony. I am going to ask you whether you agree or disagree and just to comment. This from the summary of Dr. Curran, proposed summary of testimony of Dr. Curran. It says here, according to the best recent studies of the effects of MDMA in humans, the drug's effects are relatively mild and not permanent. Do you agree or disagree?
A. No. I disagree.
Q. It further states in the summary of Dr. Curran's proposed testimony that the drug, while the drug results in impairment of human users' verbal memory, the drug's effects wear off over time and deficits in brain chemistry do not persist?
A. Again, I disagree.
Q. It further says in the summary of Dr. Curran's testimony that current studies suggest that much of what was in the report, the sentencing report, assumed to be lasting brain damage is reversible temporary impairment?
A. Again, I don't see, it's a very open question as to how

enduring it is. It's very difficult to answer that.
Q. Dr. Curran's summary of proposed testimony concludes that a reasonable scientist familiar with the research today could not reach the same overall conclusion as the 2001 report with regard to its assessment of the harms of MDMA. Do you agree with that?
A. No, I don't. I have organized a number of conferences on MDMA in recent years and nearly every paper is presenting deficits. These were all by reputable scientists.
Q. I am going to Dr. Halpern's proposed testimony as related in the summary of testimony. It says here that Dr. Halpern's proposed testimony would be that recent prospective studies on humans have not found significant changes in serotonin systems over time or evidence of permanent damage.
A. I disagree. I think the Kish study is a very good indication of damage. As to the question of permanence, that's still difficult to answer.
Q. Dr. Halpern's proposed testimony also says that, it takes issue with the report, the sentencing submission report statement that MDMA produces cognitive impairment and it says here that recent studies show, according to Dr. Halpern, that verbal problems are less associated with Ecstasy use than with other preexisting factors.
A. I don't agree with that.
MR. KOBRE: One moment, your Honor.

THE COURT: Take your time.
(Pause)
MR. KOBRE: Nothing further, your Honor.
THE COURT: Cross-examination.
THE WITNESS: Your Honor.
THE COURT: We are going to take a short recess right now for a few minutes. You may step down. We will reconvene in about five minutes.
(Recess)
THE COURT: Cross-examination, Mr. Michelman.
MR. MICHELMAN: Thank you, your Honor.

CROSS EXAMINATION

BY MR. MICHELMAN:

Q. Do you agree that MDMA is less harmful than cocaine?

A. No.

Q. But you wrote that in 2009 and again in 2010, didn't you?

A. Overall, if you combine crack cocaine and cocaine, crack cocaine is more damaging, nasal cocaine so less damaging, so it depends if you are combining the two.

Q. Just taking powder cocaine then, you are saying it's more harmful than powder cocaine?

A. It's difficult, it's even-ish. Cocaine is worse on addiction and MDMA is worse on energetic-related damage.

Q. We discussed the David Nutt study In Atlanta from 2007. You had a paper published by Addiction Today called Myth

Busters in which you critiqued David Nutt's article?
A. It wasn't my title. I wrote the article. The journalist --
Q. I won't hold you to the title but I would like to hold you to this quote. One of the things you do in Myth Busters is you rescore the drugs that Dr. Nutt considered and you rescored them using what you term the revised scores based on the empirical literature?
A. Right.
Q. In David Nutt's original study, the 2007 study, he rated cocaine the second most harmful out of the group of 20?
A. Right.
Q. He rated MDMA 18th, yes or no?
A. Yes.
Q. You write with revised scores based on empirical literature, MDMA becomes the fifth most harmful drug. It's still below cocaine?
A. Yes.
Q. Just to confirm that, you wrote in 2009, also discussing Nutt, in response to BBC journalist Mark Easton in Addiction Today, when I rescaled these scores using scientific data, then MDMA emerged as the fifth most harmful drug on this list, lower than heroin and cocaine. I will stop there. You go on to discuss other Class A drugs.
A. That's correct.

Q. So then you would agree that MDMA is less harmful than cocaine?
A. Than overall cocaine, yes.
Q. You agree generally that MDMA is not addictive?
A. No, I said it has addiction potential.
Q. Potential, but actually I think you said it was one of the least addictive drugs?
A. Yes.
Q. In fact, you began by saying it was not addictive then you discussed some ways in which it might theoretically possibly be addictive?
A. As I explained earlier, yes.
Q. You noted some dependence based on study in which the question was asked whether someone had taken Ecstasy more than once a month?
A. I am confused by that question.
Q. One of the studies you cited in support of a possibility of addiction, asked the question whether the users had taken it more than once a month, is that correct?
A. I am not sure which study you are referring to.
Q. I was reading my notes from your cross-examination. Do you believe that taking Ecstasy more than once a month is indicative of addiction?
A. I don't remember saying that in my testimony. I remember saying that those who scored high on the dependence scales

score, 20 percent of dependence users reported that they took Ecstasy more than once a week in the previous six months.
Q. But your overall conclusion is that it's not addictive but it has a potential for addiction?
A. It's not addictive in light novice users. Once people up the usage and they became heavy users, then they show dependence.
Q. Let's talk about the heavy user. I noticed throughout your testimony you broke down, you broke users down between heavy and more light or moderate users, right?
A. Yes.
Q. Now, wouldn't we expect to see more damage from any drug if used heavily?
A. Yes.
Q. Wouldn't we expect to see more damage from any medication, even a prescription medication if used heavily?
A. If it's a safe medication, hopefully not.
Q. Would you agree that most substances one could overuse them to the point that it would become dangerous?
A. I am sure we could.
Q. Even drugs that would be harmless or practically harmless in lower moderate doses?
A. I am sorry, I am lost again, a bit lost here.
Q. You would agree that heavy doses can be toxic or harmful even for substances that are not harmful if taken in a low or

moderate dose?
A. I am sure that's true of many substances.
Q. We spoke a lot about confounds and controlling for key variables?
A. Right.
Q. One of the confounds you noted that was important to control for in the MDMA context is the use of multiple drugs which we also referred to as polydrug?
A. Correct.
Q. Is it also important to control for preexisting conditions or family history of subjects?
A. It depends on the study. It depends what you are investigating.
Q. Can you elaborate on that.
A. If you are looking at how drugs affect people with problems, then you need to include them. A drug may well make people with problems worse.
Q. If you want to rule out that the drug has caused a problem, you need to control for the possibility of a preexisting problem?
A. If that's what you are investigating, yes, you would often do that.
Q. Wouldn't you always want to do that?
A. Well, if you are looking, that's an example of is MDMA causing depression. You could look at two studies, one which

looked at Ecstasy users who had no depression, such as McCann does. They screen out people with problems, with any problems. Then they found that they did develop depression. You might be interested in how MDMA may be effecting depression with people with clinical problems in which case you would include them.

Q. Unless you are investigating the effects on people with preexisting problems, you would try to exclude for the preexisting problems?

A. As I said it depends upon the study, yes.

Q. Would you also want to control for bias in the selection of the subjects?

A. Yes.

Q. I assume the best way to study effects on humans is to study, to perform MDMA studies on humans themselves; would you agree with that?

A. I guess so, yes.

Q. Could you tell us in your own words what a prospective study is?

A. A prospective study is following up people over time.

Q. Is that generally considered one of the better methods to discover the effects of a drug?

A. Some people believe prospective studies are the best. I am great believer in cross-sectional. Generally it's seen as a better standard, yes, prospective, for answering different questions, but in many instances, yes.

Q. You would agree that the NextC study is a prospective study?
A. That's right.
Q. That would be particularly valuable in studying the harms of MDMA?
A. Yes.
Q. Is MDMA safe in your view to use in therapeutic studies to investigate its possible benefits for medicinal purposes?
A. Probably but inadvisable.
Q. It's not a good idea?
A. I wrote a paper on this in 2007 where I discussed the pros and cons. My conclusion was it's probably not advisable.
Q. I would like to clarify a term we have been using throughout the day, actually throughout yesterday, the word acute. Describe what we mean scientifically when we talk about an acute effect.
A. An immediate effect. In MDMA terms, it's a few hours after taking.
Q. Acute doesn't mean serious, necessarily, just immediate?
A. Sorry?
Q. Acute doesn't speak to the severity of an effect, just the fact that it's immediate?
A. It's time-related, yes.
Q. I would like to talk about the sources that you submitted to the court in advance of this hearing in support of your

testimony. Obviously you referred to a great many sources during the course of your testimony. But you submitted six to the court in advance. These were your own study from 2001, Human Pharmacology of Ecstasy, excuse me, Human Psychopharmacology of Ecstasy, the Jansen study, Ecstasy MDMA Dependence, the Topp study from 1999, Ecstasy Use in Australia, your own study from 2006, MDMA in Humans, your own study from 2006, MDMA in Humans?

A. The review paper.

Q. Yes. Your own 2009 study regarding cortisol?

A. Correct.

Q. The 2010 Kish study regarding brain imaging?

A. Right.

Q. I assume you submitted these studies because you found them representative of what you consider a good indication of the state of the scientific field today?

A. Originally I submitted about 24 studies but my counsel said I had to reduce them.

Q. As did all the experts.

A. Which was a difficult choice. I was trying to give an illustrative overview. I had to drop some very good articles and include some qualitative articles just to give a flavor.

Q. But the six you picked you are pretty confident those give a good overview?

A. They give an overview, yes.

Q. A good one or just anyone?
A. Pretty good, yes.
Q. Three of the six articles were actually published in 2001 or earlier, is that correct?
A. If you say so. Yes.
Q. I listed Jansen 1999, Topp 1999, you 2001, you 2006, you 2009, and Kish 2010?
A. Right.
Q. We have half 2001 or earlier, half later?
A. Right.
Q. Do you think the pre 2001 studies still have a really strong bearing on what we know about Ecstasy today?
A. Yes. All information to a scientist is useful, yes.
Q. In your 2001 paper, Human Pharmacology of Ecstasy, you noted that there was a well-known reticence on the part of journals to publish findings of no harm from Ecstasy; I am paraphrasing. Is that correct?
A. That's what I wrote, yes, I believe it's still true.
Q. Given that, one might expect the literature to be skewed towards findings of harm, to overrepresent papers in which harm is found?
A. It depends on the size of the study. If it's a small study, not finding significance, a journal is likely to throw it out. If it's a large study with a large sample size, a journal is likely to accept it even if it's nonsignificant, as

in the most recent paper by John Halpern. It was a big sample size; therefore, it's accepted. Had that study with nonfindings been a small sample size, the journal would have probably rejected it.

Q. With the small sample size studies with findings of harm, the journal might well have accepted?

A. I think that's probably a bias, I guess; that would be my guess, yes.

Q. How does that affect the conclusions you gave us earlier on your direct that there is evidence going both ways on a lot of questions? Does that concern you in light of the bias that there is evidence going both ways but maybe there are some things left out?

A. If I can answer that indirectly, Rodgers et al. looked at sample size as a bias factor. They concluded that the sample size was not affecting their conclusions.

Q. So you think the Rodgers meta-analysis did a pretty good job of synthesizing this?

A. They are a bunch of statisticians so they should have done a good job, yes.

Q. Getting back to some of the papers you submitted to the court, the Jansen paper from 1999, that considered fairly extraordinary cases. It was three case studies, right?

A. Yes.

Q. One of the case studies was an individual who indulged in

binges lasting from Thursday to Monday, he was continuously awake during that time, and he also used cocaine and marijuana?
A. Right.
Q. The second case study involved an individual who injected MDMA 4 times a day and also used heroin and benzodiazepine regularly?
A. Right.
Q. The third case study was an individual who had post traumatic stress disorder and tended to take 25 to 30 tablets of MDMA per weekend?
A. Right.
Q. 25 to 30 MDMA tablets per weekend, that's unusually large?
A. It's very large, yes.
Q. The Jansen paper was basically considering outliers?
A. I guess statisticians would call them outliers; I don't believe the people themselves would call themselves outliers.
Q. The 1999 Topp study you put before the court involved a group one-third of whom had been defined by the authors as engaging in, quote, binging patterns, which the authors defined as using on a continuous basis for 48 hours without sleep?
A. Right.
Q. Many of the sample were polydrug users?
A. Yes.
Q. In fact, within the past six months, 82 percent of the sample had used amphetamines, 68 percent LSD, 40 percent

cocaine, and 17 had used heroin?
A. Right.
Q. You wouldn't consider that a study that controlled well for polydrug use.
A. It's an example of high-end users. I think I had 329 showing for a large number of people using MDMA in a pretty chaotic pattern, yes. To throw your question back, if they are outliers, it's a large number.
Q. The folks in the Topp study, many of whom binged, many of whom regularly used other drugs, you are saying they are outliers but there are a lot of them?
A. I am saying there are lots of Ecstasy users at the heavy end of the scale. As you move up the Ecstasy usage pattern, you tend to use more multiple drugs. So a lot of the heavy end users move to a more chaotic pattern.
Q. I would think it would still be hard to separate out the effects of MDMA itself when you have this, as you put it, chaotic pattern of use going on with all those other drugs?
A. Sorry, rephrase that.
Q. Wouldn't be it be difficult to separate out the effects of MDMA when there are so many other drugs going on and such heavy use?
A. In the Topp study, it would. In fact, they didn't give cognitive tests or anything. It's simply a just very descriptive study of the problems reported by these users. The

ecstasy users reported 8 physical problems on average and 4 psychological problems which they attributed to Ecstasy. These are the heavy end of the Ecstasy usage scale and they chose people using Ecstasy which they themselves state is associated with a wide range of problems.

Q. Would you say that scientific studies are more probative when the measures are conducted by scientists rather than self-reported?

A. These were interviews with psychologists, so these were interviews. The studies were funded by the Australian government so the criteria were quite straight. My recollection is that it was detailed interviews of users, I seem to recall.

Q. That doesn't quite answer my question.

A. Structured interviews, that's my recollection of how I did it.

Q. That doesn't quite answer my question. What I am looking for is from a scientific perspective, wouldn't you put more stock in a study where the scientists actually ran tests, whether cognitive tests or brain imaging or other types of scientific measures rather than simply asking people how they felt?

A. If you are interested in neuroimaging you do a neuroimaging study. If you are interested in cognition you do a cognitive study. If you are interested in what problems people are

reporting you give them structured interviews.
Q. All this study shows us is that people who use heavily and use other drugs in the meantime report a lot of problems?
A. They report a lot of problems which they attributed to Ecstasy.
Q. That wasn't scientifically verified; that was just their own view of the matter?
A. It's what they said, yes.
Q. I would like to move on to some of your discussion of the acute effects of MDMA, the immediate affects as you testified?
A. Right.
Q. You mentioned something called serotonin syndrome which you described as meaning too much serotonin in the brain?
A. Yes.
Q. You said many users experience that?
A. Right.
Q. And you said it's usually mild?
A. Right.
Q. So when someone uses MDMA there is a temporary serotonin spike then there is a return to normal?
A. There is probably a decrease in a few days afterwards, but then back to normal after 7 days probably.
Q. Thank you for the correction; I will rephrase. When users use Ecstasy, what you mean by serotonin syndrome is there is a temporary uptick in serotonin then there is a decrease in

serotonin, then about a week after use, it returns to normal?
A. Yes. So the syndrome refers to the acute period which is a few hours after taking Ecstasy when you've got a boost in serotonin. That's when people feel hot, often feel confused. They display psychomotor aspects which hit the serotonin syndrome checklist which was developed before Ecstasy was on the scene.
Q. So, as a result of this serotonin syndrome, basically you feel hot, you feel dizzy, you've got some motor coordination problems?
A. That sort of thing, yes.
Q. Let's talk about cortisol. You mentioned that another of the acute affects of MDMA is a sharp rise in cortisol?
A. Right.
Q. Cortisol is a chemical in the body that's associated with stress?
A. Yes.
Q. There are other things besides MDMA that can lead to a rise in cortisol?
A. Right, yes.
Q. Social stress might lead to cortisol?
A. All sorts of stress, yes.
Q. Let me rephrase that. Social stress might lead to a rise in cortisol?
A. Yes.

Q. Testifying in court might lead to a rise in cortisol?
A. Yes. I am glad you are not measuring my cortisol level now.
Q. Mine too. An 800 percent increase in cortisol sounds like a lot?
A. I think it is, yes.
Q. Exercise, would that increase your cortisol?
A. Yes. If you put somebody on a bicycle odometer which is one of the bikes you see in New York where people are exercising and pedal as fast as you can, physiologists call it exercise to exhaustion, so instruct somebody to cycle as fast as you can for 20 minutes, that's a standard physiological test they use in physiology labs. The cortisol rise will be about 150 percent if you are not a very good cyclist. If you are a fit cyclist, it will be about 80 percent. I cite that study in one of my papers.

(Continued on next page)

Q. How about a marathon runner after running a marathon, how high would you imagine his cortisol?
A. I am not sure.
Q. Could it get as high as 800?
A. I am not sure. I have not seen the data.
Q. Is it possible that MDMA is not the only thing that produces the rise in cortisol of the dimension that you described?
A. I have talked to a couple of hormonal people at a conference and they say it is a pretty extreme, because I didn't know that much about cortisol before I started looking into it so I started to check with some other people.
Q. I didn't know either.
But it goes away?
A. Sorry?
Q. The rise in cortisol goes away?
A. Yes. We measured for recovery in 24 hours after and it had recovered.
Q. You used the term "chemical stressor" to refer to MDMA in relation to its cortisol --
A. I think I am quoting Connors 2004.
Q. So MDMA like exercise, stress, testifying in court raises your cortisol and then it goes back to normal?
A. Yes, it will do that.
Q. Now, I would like to make sure I understand one of the sort

of general statements that you made last night at the beginning of your testimony.

You testified that all of the deficits reported in 2001 have been confirmed by subsequent studies?

A. As far as I am aware, I think they have, yes.

Q. Let's talk about what that means. Does that mean that there is some line in some study somewhere that suggested perhaps the deficit was still there, or do you mean by that something more robust?

A. Well, in science, you don't look at the individual trees, you look at the forest and sort of get an impression. And I think my impression is that those statements from 2001 have been confirmed in general terms.

Q. You have also written that the effects of MDMA are exacerbated by environmental factors?

A. That's right.

Q. So MDMA alone doesn't necessarily cause all of the problems associated with MDMA? Are you sure you can really separate the problems associated with MDMA from environmental factors and other relatively common confounds like the use of other drugs?

A. For instance, if we are talking environmentally, in the study I cited earlier, 2008 Parrott et al., Neuropsychobiology, we had the Ecstasy users go to a rave and dance, and the only drug allowed was alcohol, I think, possibly cannabis -- I have to think about that, but definitely not to have any stimulants

and their cortisol levels were not significantly altered by partying.
Q. It is interesting though, in your 2006 paper, Dancing Hot on Ecstasy --
A. Right.
Q. -- I apologize. I am sure I am leaving out the longer subtitle, you list as important factors in some of the MDMA associated problems you found, lifetime use of Ecstasy, hot and crowded conditions and the use of other drugs?
A. Right.
Q. So there are really lots of contributing factors to the problems you described as coming from Ecstasy, according to your own work?
A. There are lots of drug factors that interact with Ecstasy, for instance, alcohol increases the pleasure rating of Ecstasy. So there are reasons why people co-use drugs.
Q. You also wrote in 2006 in a study called "Problematic Versus Non-Problematic MDMA Ecstasy Use" -- bear with me.
A. Sorry. 2000 and -- is that 2001?
Q. Bear with me.
2006 article that you co-authored called "Problematic Versus Non-Problematic" --
A. Was that Soar, et al.?
Q. Let me check.
Yes.

A. That was written by one of my research students.
Q. S-O-A-R.
A. That's right.
Q. And the other authors are Turner and you?
A. Right.
Q. So you are familiar with that paper?
A. I haven't read it in a while, but I was a co-author, yes.
Q. I would like to quote from it, and I hope you will bear with me.

On page 421, you say: "The current study supports the idea that problematic Ecstasy use may be due to premorbid vulnerability in individuals, i.e., in those individuals that report problems associated with their Ecstasy use. The data indicated that a greater number of problematic Ecstasy users reported previous psychiatric history and were more likely to have a family history of psychiatric illness compared to non-problematic Ecstasy users, thus premorbid psychiatric differences may have contributed to these Ecstasy related problems."

A. That's what we found in that study, yes.
Q. When you say premorbid, what you do you mean?
A. Before taking the Ecstasy.
Q. So preexisting?
A. Preexisting, yeah.
Q. So basically you are saying that a number of the problems

associated with Ecstasy may well be due to problems that existed in the subjects before they took the Ecstasy?
A. In that study we found that, yes. What we found was that they had problems after Ecstasy, but they also had problems before. The crucial question is, what has happened to their problems.
Q. Then in the 2006 "MDMA in Humans" review that was submitted to the Court for this hearing, you pointed out that it was difficult to separate the consequences of marijuana use from the consequences of MDMA use because 90 percent of MDMA users also used marijuana?
A. It is difficult, yes, and there is high co-usage, yes.
Q. You also wrote just this year in an article entitled "Procedural and Declarative Memory" -- and again I apologize if that's not the full title --
A. That is Blagrove et al.?
Q. That's correct.
You write on page 10: "This association of recent Ecstasy MDMA use with poor declarative recall was only significant for participants who also reported having used other illicit drugs 24 to 48 hours prior to testing."
A. Yes. We found that, yes.
Q. So it sounds to me like, as a whole, a lot of the research, including the recent research finding problems with Ecstasy has been confounded by polydrug use and preexisting conditions?

A. Yes. That's what I reviewed from 2006 when I concluded there my review that cannabis was an important co-drug, that it had very complex modulator effects on MDMA. Cannabis could have had adverse effects. MDMA could have had adverse effects, and they often occur together. So cannabis and MDMA interact together in very complex ways, yes.

In the Blagrove paper we also found MDMA related deficits which were not explained by the cannabis. But some were -- it is complicated.

Q. Sure.

Now, one of the papers you placed heavy reliance on in your testimony today is the Kish 2010 brain imaging --

A. Right.

Q. We heard all of the experts who testified rely on Kish, so he is a pretty respected researcher?

A. The study we cited was evidence, yes, we focused on that study.

Q. Sure.

A. What is interesting is that Kish in 2002 he published a review where he was very quiet skeptical, he raised a question as to whether it was MDMA, so it is quite interesting that he has now published this paper showing quite very solid evidence for deficits.

Q. So in the Kish paper -- I would like to read you a quote and ask you if you agree with his conclusion and

characterization. He writes that most Ecstasy users reported "the typical acute effects of Ecstasy, including increased sociability and hyperthermia and features of a drug discontinuation withdrawal system sometimes severe, occurring one or more days after cessation of drug use and that resolved within a week"?

A. Yeah.

Q. So that is a fairly typical acute experience of an Ecstasy user, you would agree?

A. Yes. It seems to be described in fairly standard ways, yes.

Q. So the typical Ecstasy user has increased sociability, gets hotter, a few days later has a temporary withdrawal feeling but then returns to normal?

A. Yes. That would be good summarization, yes.

Q. Pardon me for one moment while I find my place in my notes. You have testified today that MDMA is neurotoxic?

A. Yeah. According to the neuroscience papers I have read it is, yes.

Q. That's the case over the long-term or just temporarily?

A. As I say, that is still to be resolved. That issue, it is not clear how long -- we need to replicate the Kish study with people who have been drug free for a while to see.

Q. But --

A. In functional terms, as I mentioned earlier, there is a

Morgan study, a Zakzanis study. It is a wide open question, but there are indicators that they are enduring over time.

Q. You wrote a paper in 2007 entitled "Ecstasy versus Alcohol"?

A. Right.

Q. And referring to serotonergic neurotoxicity, you said that there is evidence for structural recovery following drug cessation?

A. Yes. That relates to the Reneman paper where they found -- I think they reviewed six studies or five studies. And I think in four of the five, there was a correlation between duration of abstinence and degree of serotonin loss.

So in all of those studies, they showed serotonin loss but it was less in those who had been abstinent for the longest period. That is my understanding of the Reneman review.

So that, again, it doesn't show recovery because all of those studies showed deficits. So all of the studies showed serotonin marker deficits. But the degree of deficit seemed to be associated so --

Q. I just heard you say that it didn't show recovery, but in your paper you wrote: "There is evidence for structural recovery following drug cessation."

A. Yes. So in the Reneman paper, there is this correlation, so that the longer you have been off it, the less damage you still have in your system.

So the suggestion from Reneman, which I believe I was probably using for that statement, was that there may well be some recovery. But, crucially, in those studies, even those which are showing recovery, there was still impairment.

So there is indication from that literature that there may well be recovery, although people are still impaired. Basically, it is a wide open question.

We can't give particularly good evidence on that. It is all suggestive.

Q. It sounds to me like we are really narrowing down the spectrum of harms here. It used to be, we thought there was a great deal of neurotoxicity and now we recognize there is recovery and maybe just a small deficit remains?

A. Well, the animal literature has always been clear that if you stop getting MDMA, you will get what Val Curran described as pruning. So you get resurgence of axon and dendrites near to the Raphe nuclei cell. But as Val Curran noted, you don't get the full axon regeneration.

So the animal literature suggests there should be some degree of recovery, although it would suggest you won't get full recovery.

Q. So you agree then, just yes or no, that contrary to what was believed in 2001, we now know there is a good deal of recovery with respect to the axons?

A. We certainly don't know that, no.

Q. I'm sorry? Didn't you just say that?
A. You said a good deal of recovery? I said that the evidence was that there was an association between time of abstinence and degree of impairment, but even in that, the users were still impaired. So it is an association of relative. It is not a good deal of recovery.
Q. So there --
A. Most were still impaired.
Q. We now know that there is some degree of recovery?
A. From the Reneman conclusions, that would suggest some degree of recovery. Many people believe that biological systems should show some degree of recovery.
Q. Contrary to what was believed in 2001?
A. No. The animal literature prior to 2001 suggested that when animals stopped being given MDMA, you get a degree of recovery, but not permanent. That was known prior.
Q. So is it your testimony then that the scientific understanding of MDMA changes on the brain is essentially the same as it was in 2001 or worse?
A. It is very -- it is similar, but more sophisticated. So in 2001, the hypothesis was that MDMA would be causing serotonin damage in humans, and there were a couple of studies indicated that.
Since 2001, there's been a number of studies reviewed by Cowan, reviewed by Reneman. And Cowan said that the most

consistent finding is a reduction of serotonin transporter density. So Cowan's review is that there are a number of studies confirming serotonin loss in the higher brain regions. Kish is consistent with that. It is slightly better in a few ways, but it is very consistent with findings over the last 10 years.

Q. Let's hang on for a second, though. You said it was slightly better, so you would agree that the degree of serotonin transporter loss has been shown to be less than it was thought in 2001?

A. No. No.

Q. That's curious because --

A. The Kish study shows reductions of 20 to 40 percent in different cortical brain regions, 50 percent loss in the insular which is an important brain region.

Q. Let me quote to you from Kish: "We did not find a global massive reduction of brain SERT finding as reported in the first SERT imaging study of Ecstasy users," citing McCann, 1998.

A. He then discusses the reasons for that. And he also discusses why he didn't replicate Buchert et al. in 2002 or 2004 where Buchert found reductions in an area called the limbic, the striatum.

Q. That's all well and good, but what I heard him to be saying was -- and if you could tell me yes or no, am I correct -- am I

correct that Kish found less SERT finding deficits than had been understood in 2001, yes or no?
A. I would have to check the McCann paper. I would have to check that.
Q. Do you disagree with this statement from Kish: We did not find a global, massive reduction of brain SERT findings as reported in the first SERT imaging study of Ecstasy users by McCann?
A. Yes. I agree with that statement.
Q. So then it follows, does it not, that more recent brain imaging has shown less SERT depletion than was understood to be the case in 2001?
A. No. Because Buchert found reductions in the striatum.
Q. But Kish didn't?
A. Well, to answer your question. Buchert, after 2001, found reductions in the striatum. Kish discusses that study and says, for reasons, it is probably because Buchert had heavy users.
Kish then hypothesizes that their moderate users, it was affecting the highest brain regions. They were not affecting the limbic system because Buchert had higher users and McCann had the highest users.
So the two studies showing the most intense of Ecstasy users, showed regions, not only the brain cortex, but also the limbic system. And that's what McCann reported in '98.

Q. So now what I hear you saying is that Kish's work isn't of that much value because he didn't replicate McCann or the other fellow Buchert.

MR. KOBRE: Objection.

THE COURT: Sustained as to form.

Q. Are you saying that the Kish study is problematic because it failed to replicate the deficits found earlier?

A. No, not at all. It is not problematic. They discuss why they didn't find reductions in the striatum, which they predicted. And they say it may well be because their users were less heavy users than those in Buchert and those in McCann -- the Buchert post 2001 and the McCann pre 2001. So 2001 is an artificial distinction.

Q. Sure. But what I am getting at, is Kish found less damage than previous studies, yes or no?

A. No. Some previous studies found less.

Q. Kish found less damage than some previous studies?

A. Than Buchert and McCann, yes.

Q. In 2001, was McCann the major brain imaging study that had been published on MDMA?

A. I think there was the study -- was it when was that published. I am not sure. Sempel was one of the earlier studies, and the McCann --

Q. McCann was pretty well known?

A. McCann was, I believe, the first of the neuroimaging

studies. I may be incorrect on that, but that's my belief.
Q. Kish also notes, quoting from Kish -- referring to another recent study he says it "suggests that any drug-induced SERT reduction might be reversible." So again evidence for not long-term damage?
A. Yes. Most biologists believe that when you get rid of it, you will have biological recovery to an extent. It is a general biological principle.
Q. So let's talk about neurocognitive functioning. You talked a lot about that on your direct?
A. Right.
Q. In neurocognitive functioning, would it be fair to categorize all of the following areas as subfields of neurocognitive functioning: Executive function and logic, prospective memory, verbal memory and working memory?
A. Right.
Q. You have described in detail for us today a handful of studies finding problems?
A. Right.
Q. But as you yourself noted, in some of the studies you yourself cited, there were problems with the controls.
I am sorry. Let me start that question over.
But as you yourself noted, in some of the studies you yourself cited, they failed to control for important variables?
A. There is always issues over control, yes.

Q. In fact, you said that the prospective memory study by Rendell failed to insure that the Ecstasy users tested had been drug free through what you have termed the washout period of about a week?
A. No. The Rendell study only asked people to be drug free, I think, it was for one day or two days -- which is a very naive request. Most drug studies specify the drugs, don't drink alcohol for a day, don't smoke cannabis for two days, don't take stimulant drugs for a week.
Q. So Rendell failed to insure that participants were drug free --
A. In their instructions, as I say, they are very light users, either less than once a month in one group, more than twice every month in the other group. So it is unlikely that they tested someone in that washout period, although it is a possible issue with that.
Q. So we sort of have to make a leap here that they had been -- that the subjects went through the washout period?
A. I cannot imagine a research assistant bringing someone into the lab who has just taken the drug.
Q. One of your examples of an executive function and logical reasoning study, the Fisk study, you noted that there was a failure to control for polydrug users?
A. Not a failure to control for. When they looked for polydrug, they found, I think, it was use of cocaine and

amphetamine were also influential in being associated with the logical reasoning impairments, yes.

Q. Did you say that these neurocognitive impairments were long-term or acute?

A. In the Fisk study, they were all current users, but they were drug free when tested.

Q. In general, is it your testimony that the neurocognitive impairment is a long-term consequence?

A. Yes.

Q. But as you noted in your testimony, there are some reports of unimpaired performance?

A. Right.

Q. Including some of your own studies, in fact, in a 2002 paper called --

A. Is that --

Q. "Neuropsychological Evidence" by Fox?

A. Fox, et al., 2002, Psychopharmacology.

Q. That's right. You noted that "Ecstasy users remained unimpaired on most measure of pre-frontal function," is that right?

A. Yes. That was an unusual study. And Helen Fox found deficits in the temporal lobe. What she did is a very interesting study. She did the CANTAB, the Cambridge Automated Neuropsychological Test Battery, which is a standard battery of cognitive tests. And she linked up with Barbara Sahakian from

Cambridge University who had profiles for cognitive test profiles for various people with various forms of brain damage --

Q. I'm sorry, Doctor. Just for reasons of time, could we just get a yes or no: Ecstasy users remains unimpaired on most measures of prefrontal functioning, yes or no?

A. Yes.

Q. And more recently, you suggested in your 2006 paper, "MDMA or Ecstasy: The Contemporary Human -- I don't have the full title -- "and Animal Perspective," you stated, "On many assessment measures, performance levels remained unimpaired even in heavy users." Yes or no?

A. Yes.

Q. And in your 2006 review, "MDMA in Humans," which you have submitted to the Court on page 148, you state: "The literature provides extensive evidence of unimpaired neuropsychological biological functioning," yes or no?

A. Yes.

Q. In your 2010 paper on procedural and declarative memory, you stated: "The procedural memory performance of recent and abstinence, Ecstasy and MDMA users did not differ from controls." Yes or no?

A. Yes.

Q. So you have also said in your testimony that there is evidence going both ways on a lot of things?

A. Yes.
Q. Including it sounds like neurocognitive functioning?
A. Yes.
Q. So isn't it best then in evaluating this large body of literature with some times disparate results, to use a meta-analysis like Rogers?
A. Exactly, yes.
Q. Now, Rogers concludes -- and this is from the executive summary -- "The evidence we identified for this review provides a fairly consistent picture of deficits in neurocognitive functioning for Ecstasy users compared to Ecstasy naive controls.

Although the effects are consistent and strong for some measures, particularly verbal and working memory, the effect sizes generally appear to be small when single outcome measures were pooled, the mean scores of all participants tended to fall within normal ranges, yes?
A. Right.
Q. And on direct -- I believe this was last night -- you testified that Kish found memory impairments?
A. Right.
Q. But again quoting from Kish: "Nevertheless, most Ecstasy users had few cognitive complaints after the acute effect and the drug withdrawal phase had passed and user values generally fell within the normal control range, is that correct?

A. If you are reading out, yes.
Q. He goes on to state, again from page 1793, both of these last two quotes: "The observation of normal or close to normal performance on cognitive testing is consistent with much of the Ecstasy literature." Yes?
A. Yes.
Q. So it sounds to me like Rogers, who we have all agreed has done a full review of the literature encompassing thousands of studies and Kish seem to agree that -- and Kish, we have all noted is respected, and all of the experts we have relied on, everyone seems to agree overall, there are pretty slight neurocognitive effects, would you say that?
A. I think they agree that consistently significant effects, significant overall.
Q. When you say significant, you mean statistically significant?
A. Yes.
Q. But slight in terms of amount?
A. Within the normal range in that people can still function within broadly normal limits, although they are impaired.
Q. You seemed to testify otherwise, based on your own review of the literature in 2006. Do you think there's a discrepancy between your 2006 work and the Rogers and Kish conclusions we have just discussed?
A. Well, what Rogers did is took all of the studies together

and averaged them. So one of the strange things I found was that the dosage -- they were simply throwing all of the data into a great big pool and saying what is the mean score.

So in average terms, you have this slightly impaired average user. What I was doing and what most reviewers do -- the Rogers review is atheoretical. They have no theory. That is statisticians -- they are simply taking averages from everything.

What I was doing in my 2006 review is saying, we have this variation in findings. Why have we got this variation in findings? So I was taking a theoretical approach to try to explain the variance, which Rogers didn't attempt to do.

Q. What do you mean by theoretical approach? You had a theory and you were trying to confirm it?

A. As I said earlier, I was looking at what are the factors explaining the differences between studies. Why did Croft et al. in 2001 find two very different studies findings between their two studies.

And I said it may well be because one study had very heavy cannabis users and the other study had very heavy Ecstasy users. And that may well explain why one study found Ecstasy related deficits, the other study found cannabis related deficits.

So in terms of the average user, people that use very little to people that use a lot, the average effect over

everyone will be significant but not particularly marked. On a heavier user, the literature suggests, with lifetime cumulative Ecstasy use, you are more impaired. So the literature suggests the effect is stronger in those that use the drug more in their lifetime.

Q. So once again we are back to the point that, as with most drugs, if you take a lot of them they can be damaging when a small to moderate dose would not?

A. As with Kish, those with more serotonin loss showed worse memory.

Q. So yes or no, you agree that it is simply the case that higher use correlates with more harm?

A. Yes.

Q. And that is typical of most drugs?

A. Of many drugs, yes.

MR. MICHAELMAN: Thank you very much.

THE COURT: Redirect examination.

MR. KOBRE: Yes, your Honor. Thank you.

REDIRECT EXAMINATION

BY MR. KOBRE:

Q. Professor Parrott, on cross-examination counsel asked you about addiction and dependence on MDMA. Now, are there ways in which MDMA causes dependence?

A. In heavier users, they report difficulties going without the drugs. Some of them say they want to quit using the drug

but still use it. Some users report spending too much time thinking about the drugs or planning to use it. And these were reports from the Bruno study in 2008.
Q. Are there users of MDMA that are heavy users?
A. Yes.
Q. What do you consider to be a heavy user?
A. Well, the Bruno study has a table on this. Describing the group who had problems. I can't recall the details of the table, but they were heavier users compared with the group who didn't show this dependence syndrome. So some of them were using Ecstasy more than once a week.
Q. Did the Bruno group administer MDMA like in a laboratory environment or were they taking people who had actually used MDMA prior?
A. It was a survey of 1,500 people who were drug free when interviewed.
Q. So some of those 1,500 were heavier users?
A. Yes. I can't recall from their table. The only one that I can recall was, I think 60, 70 percent reported using Ecstasy more than once a week, at least once in the past six months and their lifetime usage, I recall, was heavier than those, but I cannot recall the figure.
Q. Can you give a sense of what percentage of users would be heavier users versus lighter users?
A. What percentage?

Q. Or just give a general sense of how frequently or infrequently we would find a heavier user?
A. Well, all of the studies define heavier user in different ways. It is a very sensible question, but I am afraid I cannot give an estimate.
Q. You mentioned earlier the Morgan study. Does the Morgan study have a definition of heavier or less heavy user?
A. Morgan simply looked -- Morgan strictly looked at former users v. current. I cannot remember what usage data he had in that study.
Q. You testified on cross-examination about the cognitive studies. Now, the study that you referred to on direct, the cognitive studies showing cognitive deficits, were those deficits only showed in heavy users?
A. I'm sorry. Which studies?
Q. You talked about a number of cognitive deficits about memory and what counsel referred to. He sort of lumped them all together, the memory and executive function?
A. Right.
Q. Were those deficits only found in heavy users? Are those studies all specifically with regard to heavy users?
A. No. You often find dose related effects. So in the Fox et al., 2001, that is the paper where we got the prize from the British Association for Psychopharmacology. We found that there was an increase in level of problems that you stepped up

the dosage scale. So the light users were marginally worse than the non-users. Then the moderate users were better off than the heavier uses who were further impaired.
Q. It sounds like many of these studies actually involved some heavy users?
A. Many studies have done, yes.
Q. And these were all studies where the subjects were drawn from the general population of Ecstasy users, is that right?
A. Yes.
Q. So would it be fair to say that there are enough heavy users to go around to provide --
A. I see what -- yes. In the Fox study, we took a three-way split to allocate the groupings into three fairly equal sized groups -- that's my recollection anyway.
Q. What I am getting at. You testified that in all of these studies or many of these studies, were groups of heavy users?
A. Yes. In the Fox et al. study about a third of the users -- that was my recollection -- and that was the finding using over 100 times lifetime.
Q. So is heavy use of Ecstasy rare?
A. No.
Q. Heavy use of Ecstasy is not rare?
A. No.
Q. Now, Professor Parrott, is it particularly important in trying to get at the practical effects of MDMA, is it

particularly important to control for what you refer to as premorbid psychiatric issues?
A. If you are looking at psychiatric problems, yes. You want to know, do they exist before or not, as part of your investigatory procedures.
Q. My question is, if we are trying to assess the harm of MDMA, is it important to look at both people with prior psychiatric problems and people who did not have prior psychiatric problems?
A. Yes. You have different types of study. As I mentioned before, the McCann study looked at people without prior diagnoses, and they found that taking Ecstasy led to -- it was associated with depression. And they said it was associated with binge use, so using Ecstasy for more than 12 hours was associated with later depression. And they screened out anybody with a prior psychiatric problem in that study. Also, it is very crucial because MDMA is used by people with psychiatric problems. It is crucial to know what effects, you know, to test that population.
Q. Why is that important?
A. Well, because some Ecstasy users have prior problems so we want to know, you know.
Q. What?
A. We want to know what is happening to those people. Is it worsening problems? Are the problems not getting worse? Are

they getting better. That is why it is important.
Q. Are there some studies showing that Ecstasy can actually worsen prior psychiatric issues?
A. I can't recall any that has looked at that. There are studies in psychiatric hospitals where they have looked at use of drugs and problematic drugs in the U.K.
It is a big problem, the usage of all recreational drugs by people with prior psychiatric problems. But it is actually very difficult to conduct such studies because of clinical, ethical reasons.
Q. What you are saying, the question about whether Ecstasy use can worsen or somehow interact with prior psychiatric problems, that question has not yet been answered in scientific literature?
A. It would be nice to be able to look at that. I cannot off the top of my head recall such a study. They may well exist, but at the moment I can't recall any.
Q. Would it be a problem if Ecstasy use worsens prior psychiatric problems?
A. If that was found, it would be a problem, yes.
Q. Now, counsel on cross asked you about some of the articles that were submitted to the Court, some of the six articles. What were your criteria for choosing those articles?
A. Well, I have been criticized for choosing the Jansen article, and I couldn't decide whether to include the Bruno

article which is in Australia on the sample of 1500 versus the case study. But I included the case study because it illustrates the sort of intensive usage you do find in some people at the extreme end of the spectrum. So it shows that MDMA is problematic for people at the heavy end who are using it in a very problematic way.

Q. And these people at the heavy end, putting aside Jansen, sort of just heavier use, what's been talked about heavier use in the papers, how commonly does that occur?

A. It is quite rare because most people quit using the drug before that stage.

What you tend to find is people have a honeymoon period when they start taking the drug, where it is very few problems. And then they go through a stage of intensifying their use, they have a chronic tolerance.

Then they either decide to quit because it is causing more problems than gains, or they carry on using, in which case they need to move up to the heavy end of the usage spectrum, and then they will often use it with multiple other drugs.

Q. During the period of intensifying use, would those people be considered heavy users?

A. Yes.

Q. Does that happen pretty commonly?

A. As I say, it is one of those drugs which is very strange in that people tend to take it less frequently over time. This

has been found in a couple of studies, which is very unusual for drugs.

So what seems to be happening, they are developing more problems. They are developing more problems. They then develop these desires to have the drug, but they are having problems with the drug. So have this balancing effect of cost-benefit ratio so they are taking it less frequently, but still go back to using.

It is very strange for a drug to be used less intensively over time. Most users then quit although some people will continue intensifying their usage.

We tested one such person, and that was published in Soar et al. My research assistant tested someone who used very heavy Ecstasy for three years. It was massive problems. They have been abstinent for seven years, and they still have these problems. They had wide-ranging problems. In the intervening years they were heavy users of multiple drugs. So it is a very chaotic pattern.

Q. You mentioned on cross-examination that lots of Ecstasy users are at the heavy end of the scale?

A. I'm sorry?

MR. MICHAELMAN: Objection. Mischaracterizes his previous testimony.

THE COURT: Why don't you just put a question to the witness.

BY MR. KOBRE:

Q. In your study about cortisol that we discussed on direct, you were asked on cross about whether that cortisol effect goes away, it is only there in acute stage. What are the long-term effects, though? Are there long-term effects of the acute cortisol increases?

A. There is a study by Gerra et al. -- I think it is 2002 -- which looked at cortisol levels in drug free, abstinent Ecstasy users, and I think they found a deficit in users. But I think they also replicated the study on other occasions and didn't find a deficit. So it is unclear about the long-term effects on cortisol.

Q. I think you were asked on cross-examination whether these increases in cortisol are just like exercise. Are the increases in cortisol that you found in your study as a result of MDMA use, are they similar to the ones that are typically found in exercise?

A. No. They are far stronger. And one of the problems of MDMA is that it tends to stimulate release of all neurohormones. You get a release of testosterone. You get a release of progesterone, prolactin -- a whole range of hormones are increased by acute MDMA.

Q. Counsel asked on cross-examination about your testimony that sort of the harms that were associated with MDMA before 2001 having been confirmed. Were there studies subsequent to

2001 confirming, for example, the cognitive deficits that you testified to?
A. Yes. Many studies since 2001 have found cognitive deficits.
Q. And those are studies specifically to determine whether MDMA use -- were those studies specifically to determine whether MDMA use impairs cognitive ability?
A. Yes. There have been lots of studies saying there is an association between Ecstasy use and cognitive deficits, yes.
Q. Professor Parrott, you were also asked about the effect of environmental factors?
A. Right.
Q. Is it important -- are the effects of environmental factors important when looking into the harms of MDMA?
A. Yes. There's an animal study. I cannot remember the authors now, but they found when laboratory rats were given MDMA, it is more re-enforcing in the heat, in other words, the rats button press more for the drug.
Q. Turning to the humans, if we are interested in determining how harmful MDMA is to humans, is it important to look at humans in the typical environment in which MDMA is used?
A. I believe it is, which is why we do those studies.
Q. Why is that?
A. If MDMA is more enforcing in the heat, the theory is that Ecstasy users may find more pleasure when they become hotter.

So it is not just the drug itself, it is the drug plus the heat. So it may well be the reason for the association between MDMA and raves is that raves provide the ideal environmental conditions to boost the effects of the drug.

Obviously if you are boosting the effects of the drug, that may well have an acute increase, but it may well lead to problems later. And that is what we have found in a study we published in 2006 in the journal Human Psychopharmacology called Dancing Hot on Ecstasy.

Q. So actually in assessing the harms of MDMA, is it actually more important to assess them in the environment this which MDMA is typically used?

A. I think it is probably more damaging in the hot environments of raves than it is in the laboratory. What we found there was that people who danced continuously or felt hot reported more problems the days afterwards.

Q. You were asked about the Soar et al. study?

A. Right.

Q. And could you describe what the methodology and the conclusions of that study were briefly?

A. I hadn't read that study for many years, so I am afraid I can't answer that.

Q. Professor Parrott, I think you spoke with counsel about the question of whether there is recovery to the serotonin neurons. Can you explain whether there is recovery and whether recovery

proceeds to baseline, whether there is full recovery, how that occurs?
A. It is my understanding, based on the Reneman review of 2006, people were still impaired.
Q. Is that in each of the studies that Reneman looked at?
A. My recollection of Reneman review was that they found consistent finding for damage.
Q. Does that imply anything to you with regard to whether there is recovery at the baseline?
A. As I say, the studies have yet to be performed to follow up users over many times, but certainly the studies covered in various views which are on current users or people who have not used for a fairly moderate period of time rather than long period of time, show that the deficits are there.
Q. You mean that the deficits remain?
A. The deficits are there for the limited period of time that people have studied.
Q. Could you tell us how, with respect to the deficits in serotonin transporter and the axon damage, has there been any kind of significant change in the scientific consensus of scientific opinion prior to 2001 versus after 2001 and up to the present?
A. Well, prior to 2001, the evidence is very limited, but since then, the broad general findings have been confirmed.
Q. And those findings are?

A. That reduced serotonin in the cerebral hemispheres in many studies and some studies also show deficits in the subcortical deficits of the limbic system, but not all studies show that.
Q. I think that you were asked about Kish and your conclusion that Kish didn't find a global decrease in SERT. What does that mean?
A. Well, in Kish's discussion he said, we predict to find deficits in the striatum, which is a part of the limbic system. They didn't find that, and they were surprised by that because Buchert had found that and McCann had found that.

So they then looked at the McCann and Buchert papers, and they hypothesized that it may well be because Buchert and McCann had used heavier users and that there are a couple of sentences in the Kish report which says that there were some indications in the Kish study that their heavy users may well have had the start of a deficit in the striatum, but they didn't present any data, it was just a sentence in the discussion.
Q. Did Kish find that other parts of the brain were affected?
A. Kish found that all areas of the cerebral cortex were affected and the hippocampus. So those were the two brain areas but, obviously, the cerebral cortex is the vast majority of the brain.
Q. What Kish found was there were some parts of the brain that were not affected but other parts were certainly affected?

A. Yes. So the traditional areas for deficits were confirmed in the Kish study. And one finding they found was that the insular which is a very small part of the brain in the region between the frontal cortex and the temporal lobes. It is a tiny area. The reduction there was 51 percent, which is a very big reduction.

And they say that is important for awareness, which I was intrigued by because in the Helen Fox study published in 2001, we found that Ecstasy users had memory problems and reported that they didn't have problems related to Ecstasy. So when I saw that, I was quite intrigued as to whether that might explain some of the Fox findings.

Q. Counsel also asked you about some of the neurocognitive studies and whether they controlled for confounding factors.

Let me just run through very quickly the sort of the major areas that we talked about and ask you about whether there are studies with respect to each of them that did sort of control for polydrug use.

Verbal memory?

A. They have investigated it, yes.

Q. They have controlled for polydrug use?

A. They have investigated the effects of polydrug use and find the deficits despite controlling for polydrug use.

Q. Is the same true for prospective memory?

A. I believe Heffernan has controlled for that, yes. And the

Reneman study had co-use of cannabis as a co-variant because they were heavy users of cannabis, and in Reneman they controlled for co-variants but the deficits still remained with respect to memory, yes.

Q. Executive function?

A. I am sure there have been studies. I can't recall --

Q. I think that you were asked on cross-examination about the Fox study. Could you just explain the methodology of Fox and what was actually found in that study?

A. Fox et al., 2001 I have already talked about. This is Fox et al., 2002. And she had the very good idea of comparing the cognitive profiles of Ecstasy users versus those with brain damage. And so she linked to Barbara Sahakian from Cambridge University who had given the CANTAB, Cambridge Automated Neuropsychological Test Battery to various groups of brain damaged patients at Cambridge University. And they had different profiles for people with different areas of brain deficits.

And when Helen did her 2002 study published in Psychopharmacology, she found the deficits of the Ecstasy users were similar to those with temporal lobe damage. That is the area of the brain which was the side which was responsible for memory, closely linked with hippocampus action. But she didn't find deficits in tasks, frontal deficits, which we had expected but that didn't occur in that study.

Q. But she did find some deficits?
A. She found deficits similar to those with people with temporal lobe brain damage, yes.
Q. Counsel asked you about your 2006 review paper?
A. Yes.
Q. In that paper, counsel sort of related that you had provided some examples in that paper of evidence showing lack of impairment?
A. Right. In the 2006 review.
Q. But did you cite studies in that paper showing impairment?
A. Oh, yes.
Q. So really what was the purpose in writing the paper?
A. It was to try to look at some theoretical reasons why we have such variance in findings. As I think I mentioned earlier, a lot of the papers could be explained in terms of whether people were light or heavy users and, also, the co-various drugs were often modulated for findings in very complex ways.
Q. The cognitive deficits that we have talked about this morning, would they have an effect on people's everyday lives?
A. I am afraid so, yes. I have mentioned the prospective memory. If I can give a sort of case report --
Q. Can I just ask, because counsel related that some of the findings were that there was significant impairment, significant statistically, but still within normal range.

A. Right.
Q. Can you comment on that?
A. If I can give an example, in 1999, when we were still at the early stage of doing these studies, we had someone phone up the laboratory and said they wanted to be tested. My research assistants were busy and they could only come in the evening, so I stayed behind at the office and met this Ecstasy user and his girlfriend. And he was very interesting. I ended up interviewing him for a couple of hours.

He was a regular user of Ecstasy, had used for a couple of years and he then went on holiday, and he used Ecstasy every night, and he took it and partied.

I don't know if I am allowed to swear in court, but he said to me, "I woke up one morning and realized that I had fucked my brain up" -- direct quote.

I said, what do you mean by that?

He said, well, I just couldn't remember anything. And he said, I was really scared. And over the ensuing days, my memory came back. But since then I have not taken Ecstasy.

I said, how long ago was that?

He said nine months.

I said, why did you come to see us today?

And he said, well, my girlfriend has been nagging me to see somebody because he kept on having these severe memory lapses.

And I said, why did you come to see me what made you come?

He said, last week I was at a business meeting. And he runs a music business with a friend and they had a business colleague come and chat with them. And he said he greeted them at the door, put out his hand, went to shake his hand and said, hi, my name is - and he had forgotten his own name.

And he then said my name is Bob -- and he had forgotten his own name -- which is a friend of his business partner. So Bob looked at him, and the guy shaking his hand looked at him and as he said to me, I didn't get the contract. But he said, then I realized I had problems.

So I tried to interview him. I tried to offer him help. I offered him to come back, but he wanted instant -- he said, can you solve my problems? I want you to solve it?

I explained I couldn't. So if he had come back, I would try to link him up with psychiatry and a therapy group, try him with memory strategies, etc., but he didn't come back, although I had urged him to.

That's the most severe example. And it was then that I realized that these memory problems can be quite marked. They were just not trivial. Some people are suffering.

Q. So does the fact that somebody's memory may sill be within the "normal" range, does not that mean it does not have any practical effect on their practical day-to-day abilities?

A. Certainly in some people it does have practical adverse effects. I also asked him about cannabis. He tried it and he didn't like it. He said that the only drug he took regularly was Ecstasy. He liked Ecstasy, but he wasn't a polydrug user.

MR. KOBRE: Just one more moment.

THE COURT: Take your time.

MR. KOBRE: Nothing further, your Honor.

THE COURT: Mr. Michaelman, do you have more than a few questions on recross?

MR. MICHAELMAN: Not more than a few.

THE COURT: Then why don't you proceed now.

RECROSS EXAMINATION

BY MR. MICHAELMAN:

Q. Dr. Parrott, just briefly, on the question of heavy users which is discussed on the redirect, just because heavy users are available for studies doesn't mean that whoever comes to the studies is necessarily representative of users in the population as a whole, correct?

A. Yes.

Q. Just to reiterate something you said on redirect, you actually don't know what percentage of users are heavy users?

A. No.

Q. Finally, just on the issue of controlling for preexisting conditions such as psychological problems, if a study has not controlled for preexisting psychological problems and then test

users and then finds harms, we don't know whether the harm comes from the use or the prior psychological problems, is that fair to say?
A. Yes.
MR. MICHAELMAN: Thank you.
THE COURT: Anything further?
MR. KOBRE: No, your Honor, thank you.
THE COURT: Dr. Parrott, I have some questions for you, but I think that I am going to put them to you after our luncheon recess. Are you able to return after the luncheon recess?
THE WITNESS: Yes.
THE COURT: Can we resume at 2:10, take a somewhat shorter --
MR. MICHAELMAN: Of course, your Honor. I would even be fine with starting at 2.
THE COURT: What about the defendants?
MR. RORTY: 2 o'clock is fine. That will help insure that we conclude today.
THE COURT: Obviously, if it is necessary for us to work beyond 5 o'clock to complete the hearing, we will do so because I am sure that these folks have schedules and planes to catch, among other things.
MR. CHUNG: That they do.
THE COURT: At this juncture, do the defendants

anticipate recalling either of your experts at the conclusion of the government's presentation?

MR. RORTY: Not at this juncture, but that is subject to Professor Hanson's testimony.

THE COURT: Then we will take an abbreviated lunch. I will see you all at 2 o'clock.

You may step down.

(Witness excused)

(Luncheon recess)

(Continued on next page)

AFTERNOON SESSION

(2:00 p.m.)

THE COURT: Dr. Parrott, prior to your engagement by the government in connection with this matter, were you familiar with the Sentencing Commission report to Congress in 2001?

THE WITNESS: No, your Honor.

THE COURT: You have reviewed the Sentencing Commission report?

THE WITNESS: Right.

THE COURT: The Sentencing Commission placed significant weight on studies by George Ricaurte. Have those studies been discredited?

THE WITNESS: There was one study by Ricaurte in Science which was retracted where he reported dopamine neurotoxicity and that was retracted, yes.

THE COURT: Is there any other science that's cited in the Sentencing Commissions report that does not hold true today from your perspective?

THE WITNESS: No. I believe the main conclusions are consistent.

THE COURT: In preparing for your testimony here, have you become familiar with the sentencing guidelines?

THE WITNESS: I have had seen them, yes.

THE COURT: You understand that there is a methodology

utilized by the Sentencing Commission for determining equivalent drug weights for the purposes of imposing sentence?

THE WITNESS: Right.

THE COURT: Do you recall in the report that the Sentencing Commission said it shows a greater penalty structure for MDMA than for powder cocaine?

THE WITNESS: Right.

THE COURT: The Sentencing Commission did so for three principal reasons which I would like to ask you about. The first reason that the Sentencing Commission proffered was, and I will quote, unlike MDMA, powder cocaine is not neurotoxic. Do you agree with that conclusion?

THE WITNESS: I have not studied cocaine so I can't really answer that. I don't believe cocaine is neurotoxic, but I have not looked at that literature.

THE COURT: In your work with MDMA have you become familiar with the marketing of MDMA?

THE WITNESS: I have not really done research into that, no.

THE COURT: The second reason that the Sentencing Commission offered to Congress was that powder cocaine is not aggressively marketed to youth in the same manner as MDMA. I take it that you are not in a position to express any opinion at all with respect to that point?

THE WITNESS: Yes, I cannot.

THE COURT: But can you tell me something about what the age profile is for a typical MDMA user?
THE WITNESS: Typically late adolescence early adulthood.
THE COURT: How does that compare to other drugs, especially cocaine?
THE WITNESS: In the U.K. I think the target audience is fairly similar.
THE COURT: The Sentencing Commission offered as its third reason that powder cocaine is only a stimulant but MDMA acts not only as a stimulant and a hallucinogen. Do you recall reading that?
THE WITNESS: I read that, yes.
THE COURT: You heard Dr. Halpern's testimony yesterday that the notion that a stimulant plus a hallucinogen means something more than just a stimulant?
THE WITNESS: Right.
THE COURT: Do you agree that the fact that MDMA is both a stimulant and a hallucinogen is a matter of significance in comparing it to cocaine?
THE WITNESS: Its main effects are as a stimulant. The hallucinogenic properties are really quite mild.
THE COURT: Would you characterize MDMA as a hallucinogen?
THE WITNESS: As I say, it can have hallucinogenic

properties but they are very mild compared with the standard hallucinogens. I would characterize MDMA as a stimulant and energetic stressor rather than a hallucinogen. I think those aspects are quite mild.

THE COURT: How many doses per gram are there in a gram of MDMA?

THE WITNESS: How many tablets?

THE COURT: Yes.

THE WITNESS: In the U.K. it's thought to be around about 70 milligrams per tablet.

THE COURT: Is that the average, about 70 milligrams?

THE WITNESS: That's the estimate.

THE COURT: As part of your work have you ever conducted any chemical analysis on tablets to determine what the weight composition of MDMA is?

THE WITNESS: No.

THE COURT: Does an Ecstasy user typically take only one Ecstasy pill?

THE WITNESS: No. They take one as the first instance typically, but then they typically increase their dosage. So, regular users may well take 2 or 3 tablets. As they become heavier they might take 6 tablets. Occasionally people take 10 or more.

THE COURT: Would they take those tablets all at one time?

THE WITNESS: It varies. Generally they take them successively. Heavy users might take a couple of tablets to start with then one a few hours later, one after that successively. They also take MDMA powders, particularly if they are experienced users. That's in a larger amount.

THE COURT: Can you tell me how many doses there are in a gram of cocaine?

THE WITNESS: No, I am afraid not.

THE COURT: How about marijuana?

THE WITNESS: Again, I am not sure.

THE COURT: In determining the harm posed by MDMA, is it appropriate in your view to consider emergency room visits or deaths associated with the use of the drug?

THE WITNESS: Yes, that could be a factor, yes.

THE COURT: In your view is cocaine more dangerous or less dangerous than MDMA?

THE WITNESS: The problem with cocaine is it's far more addictive than MDMA. The problems of cocaine use is far more apparent. It's basically what you see is what you get with cocaine. You see problems. MDMA is a far more subtle drug, so the dangers of MDMA are more pervasive on a wider range of functions. But people will be impaired in various things but it won't be as severe as many of the problems of cocaine, particularly in terms of addictiveness. It's a difficult question to answer.

THE COURT: I understand it's a difficult question; I have to press you on it.

THE WITNESS: Right. We have done a recent survey where cocaine use has become more prevalent in the U.K., just a couple very small studies, very small end. We asked people, cocaine users and Ecstasy users, the same set of questions. In this study the damage and acute effects of the drugs are quite similar. They both reported memory problems. But the midweek problems were more marked in the Ecstasy users. I think MDMA has more enduring effects over time, particularly in recovery.

But there is large literature showing cocaine is more addictive and its addictive properties in that aspect make it more problematic. Some of our Ecstasy users in the interviews conveyed problems getting into work on Monday, stuff like that, which you tend to get in connection with cocaine and with MDMA, but it's duration of the recovery period.

THE COURT: Have you familiarized yourself with some of the studies that have been submitted to the court showing that the number of emergency room visits relating to cocaine far exceed the number associated with MDMA?

MR. MICHELMAN: I have seen that literature. One aspect of that is MDMA is often taken at raves and you often get triage at raves so you have paramedics attending raves. The burning man festival was mentioned earlier, so you have medics there. It may well be a fair number of MDMA users visit

the paramedics then rest and then recover in that medical sense which is possibly not recorded on hospital data. That may be a factor; I don't know.

THE COURT: You mention in your testimony that MDMA's properties may be enhanced by heat?

THE WITNESS: Right.

THE COURT: By being in a warm place?

THE WITNESS: Right.

THE COURT: Are there any studies that have compared whether there is more MDMA use in a warmer climate or during the summer as opposed to the winter?

THE WITNESS: I don't know those studies.

THE COURT: The defendants' experts have argued that MDMA fatalities are rare. Do you agree with that?

THE WITNESS: Yes.

THE COURT: In determining the harm posed by MDMA, is it appropriate to consider the potential for addiction?

THE WITNESS: Yes.

THE COURT: There was also reference to a study that you conducted of ranking the drugs by the degree of harm and would you just report to me what it was that you concluded in that study about MDMA in comparison to cocaine?

THE WITNESS: Cocaine was ranked second. I ranked MDMA fifth in that paper.

THE COURT: What were the other drugs you ranked if

you can recall from one up to five.
THE WITNESS: I would have to check the paper. It included things like tobacco, CAT, which is a herbal stimulant, methadrone I think was another one. I don't think we had methamphetamine, but I can't recall anymore.
THE COURT: Dr. Curran testified that the prevailing consensus regarding the neurocognitive effects of MDMA is that MDMA causes relatively minor but statistically significant neurocognitive effects. Do you do agree with that?
THE WITNESS: In light and moderate use the effects are significant and quite mild; in heavy users they are slightly stronger.
THE COURT: When you use the word significant there, you are referring to statistical significance --
THE WITNESS: Yes, I mean --
THE COURT: -- or not. Tell me what you are referring to.
THE WITNESS: Well, both. So, it is statistically significant, but it does have everyday lifetime implications. So, for instance, with respect to memory, if you are missing appointments with your boss, your boss is not going to be too happy, and so it has everyday implications. It may not be major implications but it certainly is going to adversely affect your lifestyle if you are missing a proportion of future memory appointments.

THE COURT: Yesterday Dr. Curran analogized it to having a grocery list with 30 items and forgetting one item --

THE WITNESS: Right.

THE COURT: -- at the end of the day and she characterized that, let me characterize it as minimal. I think she said that it fell within the normal range of functioning. My question for you is do you agree with that analogy by Dr. Curran that the cognitive impairments, while they are there and they are statistically significant, they still fall within the range of normal everyday functioning?

THE WITNESS: If I can cite and reply the Morgan study that looked at former users. They controlled to record 8.5 items of information. The former Ecstasy users in that study reported 4.5 items of information. That was a fairly substantial relative deficit. Certainly interviewing Ecstasy users, they do report practical implications of memory loss is adversely affecting their everyday life.

THE COURT: Do you agree with Dr. Halpern's testimony yesterday that the brain changes noted in MDMA users are comparable to FDA-approved SSRIs?

THE WITNESS: No.

THE COURT: Can you explain why not.

THE WITNESS: I think that the deficits, if you got these deficits in a prescription medicine, it would never be passed. We focus on the neurocognitive. There are other

deficits. One thing we have not mentioned is sleep apnea. In a study by McCann, she recorded an increase of sleep apnea in young Ecstasy users and sleep apnea is traditionally a disorder of middle-aged overweight predominantly males. And they found it in young not-overweight Ecstasy users.

The thoracic surgeons involved in the study were not surprised. They said serotonin is involved in the control of breathing, including breathing during sleep. That's a genuine practical problem for youngsters. It's not just cognition. It's the Connors immune incompetence. It's the reduction in efficiency of white blood cells, those sorts of things, hormonal changes. MDMA is a very powerful drug; it affects a whole range of neurotransmitters. We focused on serotonin. It also stimulates dopamine and that has adverse effects.

So it's a very different drug from cocaine. It's very different to quantify. The effects of MDMA are more subtle. In my assessment they are more pervasive because of a general lowering of cognition and bodily functioning. In a recent study, Scully et al. published 2010, which was looking at hair analyses primarily, we asked about happiness ratings in Ecstasy users and they were lower than the controls. This fits in with the earlier study of Parrott and Lasky whereas the weight Ecstasy users take and you may feel better, paradoxically over the week they feel worse because the positive effects last a few hours, the negative effects last a few days.

If you've got a regular Ecstasy user their overall moods are overwhelming. In the same study we found high stress levels in Ecstasy users, self-reported stress. So this regular stress, energetic stress of regular MDMA use is leading to a range of subtle but damaging effects upon human functioning. It's not just neurocognition; it's other everyday happiness, sleep, occupational problems have been related, interpersonal problems. Also when you become a heavy user, aspects of dependency, people spend too much time.

In the conference paper in Australia, the conference I organized in Australia this summer, there was a paper by a user group. They reported financial problems, that they were spending so much money on Ecstasy that when eventually they quit in their mid to late 20s, they didn't have the money, they hadn't got any savings because they had been spending their money on Ecstasy over those period of years. As they became tolerant, they were spending more and more of their money on the drug. So it's a wide range of issues to consider.

THE COURT: There also has been testimony from various witnesses about recovery. What is the prevailing consensus regarding recovery of the brain in years following MDMA use?

THE WITNESS: This isn't really my area. I have been reading this area before this meeting, so I am rather limited on the papers. I have not really read the papers on recovery. But talking to Valerie Curran at lunch, she said there were

papers indicating recovery. I am not really aware of those papers. But I was more aware of the paper showing damage, the Kish paper. I think that's something I would like to clarify for myself.

THE COURT: On cross-examination today you talked about studies and sample sizes where if there is a harmful effect that's reported, it may be more likely that a smaller study will be published than if a similar-sized study did not show any harmful effects. My question is do you find that that is true with respect to all drug studies?

THE WITNESS: I think that's true with any scientific trial. If you have a small sample size, any journal is likely to reject it; they like a larger sample size.

THE COURT: I appreciate that point. I am moving to the next point which was that it's more likely that a smaller sample-sized study would be published in a journal if it showed a negative or harmful effect as opposed to a similarly sized study that didn't showed such an effect.

THE WITNESS: There is a statistical reason for that in that it's called the power of the effect. If you have a small sample and you show an effect, that means you have a genuine validity of that study to generate the finding. If you have a small sample and you don't defect the effect, it may well be because statistically there is not enough power in that design. So there is a reason why you would have a biased

publication rate for small studies. They are more likely to accept positive results rather than negative for that statistical reason.

THE COURT: Thank you, Dr. Parrott. Do counsel have any questions they would like to pose to Dr. Parrott in view of the court's inquiry.

MR. MICHELMAN: We have a few, your Honor.

THE COURT: All right.

RECROSS EXAMINATION

BY MR. MICHELMAN:

Q. You mentioned that the 70 milligram dose was the usual dose for a tablet?

A. Right.

Q. A human might begin with one dose or maybe over the course of night take 2 or 3?

A. Right.

Q. So in terms of a measurement we have talked about over the course of the last two days, milligrams per kilogram, what would one tablet of 70 milligrams translate to in terms of milligrams per kilogram in an average human?

A. I need pen and paper to work that out. Sorry, 70 milligrams, I guess 70 kilograms, an average person --

Q. 70 kilograms is about 150, 160 pounds?

A. Yes. We are bit smaller in Europe.

THE COURT: We supersize everything over here.

Q. About 1 milligram per kilogram would be a typical human dose?
A. Yes.
Q. The judge asked you about conclusions in the 2001 report and whether they hold true. Some of the science there relied on animal studies where the animals were given much higher doses in terms of milligrams per kilogram; 10, 20 milligrams per kilogram. Would you agree that those doses are no longer representative of average human use?
A. If you use interspecies scaling, the standard pharmaceutical formula, then the dosage would be within that range. But there are some studies since that, I can't recall the names, but a paper published in 2006 or 2007 by animal researchers where they had used lower doses with animals and they found deficits with the animals with lower doses.
Q. In terms of the propriety of the dosing, you are aware that the principles of interspecies scaling used by Ricaurte and others around 2001 have come under serious criticism?
A. I believe the same interspecies scaling formulas are still used by the pharmaceutical industry today as they were then; I don't think they have changed.
Q. In spite of criticism by Dr. Baumann of NIH?
A. I am not aware of that, my understanding.
Q. You mentioned with respect to the ER data that that might be useful to consider in terms of the harms of MDMA but that we

couldn't rule out the possibility that Ecstasy users would be attended to by paramedics rather than emergency rooms?
A. Right.
Q. But that's just really speculation on your part?
A. It was a paper by Suy et al., a Dutch group who went to a as massive Dutch rave in 1999. They had a triage, medical triage. They treated about 150 people at the rave. I think they reported that none of those people needed then to go to hospital. So the triage of a rave was dealing with the problems.
Q. Are there any studies then showing the degree to which potential emergency room visitors out of an MDMA user population would be diverted to triages at raves and then not go to an emergency room?
A. I don't know of other systematic surveys. I just know that it's a fairly common phenomenon at raves to have these medical facilities.
Q. You mentioned the Morgan study to discuss cognitive impairment. What is the date of that study?
A. Morgan, 2002, I think.
Q. On cross-examination you spoke highly of the NextC study which was a large prospective human study in the Netherlands published in 2007?
A. Thelma Schilt, yes.
Q. So that's a pretty good study?

A. Yes.
Q. I believe that's where Dr. Curran got her one item out of the grocery list of 30 words from?
A. I think in that study, I am not sure where she got the one in 30; it may well be that study.
Q. The later human prospective study supports Dr. Curran's conclusion that the effect would be as slight as one item out of 30?
MR. KOBRE: Objection.
THE COURT: Sustained.
Q. Would the Schilt paper support the notion that an Ecstasy user might only forget one item out of the list of 30?
MR. KOBRE: Objection.
MR. MICHELMAN: On what grounds.
THE COURT: No. Sustained as to form.
Q. Are you familiar with the Schilt study?
A. Yes.
Q. In your view would the Schilt study support the conclusion that an MDMA user might forget only one item out of a grocery list of 30?
MR. KOBRE: Objection.
THE COURT: Overruled. He talked about another study. He talked about a study on direct and on my examination where there were 8.5 items and an Ecstasy user only could remember 4.5. We have had testimony about this grocery list and it's in

the study. I think he can comment on it.
MR. KOBRE: I think the witness testified that he didn't really recall the contents of the Schilt study.
THE WITNESS: I do recall the Schilt study.
THE COURT: There we are.
A. The Schilt study involved youngsters, I think 16 and 17 year-olds, and they used 3 tablets. So, after 3 tablets, if they have a memory loss of one word is quite impressive.
Q. But that's what the study showed?
A. Yes.
Q. My final question is about the possibility of long-term cognitive impairment. You mentioned you believe Ecstasy does cause functional cognitive impairment in individuals. You gave us examples, some anecdotes from your own experience where study participants might forget to turn up for studies or forget their own names. Are there any studies supporting this phenomenon or are you just relying on those anecdotes?
A. Again, the Morgan study which I cited earlier would be empirical support.
Q. For long-term?
A. For long-term. These are former users who recalled on average 4.5 items of information compared with the controls who recalled on average 8.5.
Q. You would stand by that in spite of the Schilt study?
A. They are independent studies; they are unrelated to each

other. They both have got their own function, yes. The Morgan people had used a lot more Ecstasy.

Q. That's interesting. So would you consider the Morgan participants heavy users?

A. They have been using, yes, I can't remember whether they were users. I think it was just a one standard use group. It was one group of former users.

Q. Had they been heavy users?

A. I can't recall their criteria in the paper.

MR. MICHELMAN: Thank you.

MR. KOBRE: Just one.

Q. Has the Morgan study been called into question at all or been discredited?

A. No.

MR. KOBRE: That's all.

THE COURT: Thank you.

You may step down. You are excused.S.

(Witness excused)

THE COURT: Would the government call its next witness.

MR. CHUNG: The government calls Glen Hanson.

GLEN ROY HANSON,

called as a witness by the Government,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. CHUNG:
Q. Tell us about yourself; tell us about your education.
A. I have a PhD in pharmacology and toxicology that was received at the University of Utah. I have a DDS degree, a doctorate in dental surgery, that I received at UCLA. I did a postdoctoral fellow at NIH in neuropharmacology. I am currently a full professor, a tenured professor at the University of Utah, director of the Utah Addiction Center, senior advisor to the director of the National Institute on Drug Abuse at NIH, which is the National Institutes of Health in Washington, D.C.
Q. National Institute on Drug Abuse otherwise known as NIDA?
A. NIDA, that's correct.
Q. What other affiliations have you had with NIDA?
A. I was director of the division of neurobiology and behavioral science research and I was the acting director of the institute from 2001 to 2003.
Q. What is NIDA?
A. NIDA is a federal agency. It's one of the NIH institutes. It has the charge or mission to fund research from very basic molecular genetic-type of research all the way up to clinical or translational research with the intent of identifying issues and biologies and hopefully therapeutics that would be useful in treating problems associated with drug abuse.
Q. Is it true that NIDA is the single biggest funding source

for those subject areas that you just catalogued?
A. That's correct. NIDA funds approximately 85 percent of the research that relates to substance abuse in the world.
Q. What are your general areas of research?
A. My particular specialty are the psychostimulants in particular. We research amphetamine or phenylethanolamine drugs. So that would be amphetamine, methamphetamine, MDMA or Ecstasy, and analogs associated with those drugs. We also look at cocaine and we have done research on PCP, heroin, and we are also interested in some neurobiological things that relate to diseases such as schizophrenia and Parkinson's Disease.
Q. When did you start researching MDMA in particular?
A. We became interested in MDMA in 1985, '86, when the first epidemic of Ecstasy abuse was occurring that started in Europe and had moved across the ocean. We were seeing a significant use by young adult populations. Because of its apparent relationship, molecular relationship to the amphetamines, we were interested in what it might look like as pharmacology and its short and long term effects on neurosystems.
Q. You have been researching MDMA for the last 25 years?
A. That's correct.
Q. Have you published any studies or papers relating to MDMA's physical effects?
A. In 25 years I would hope we got something on it. Yes, we have published 30 to 40 papers that have been in scientific

peer reviewed journals.
Q. Are you yourself on the editorial boards or boards of any peer reviewed journals?
A. Yes, I review for many of the top pharmacology and neurobiological journals.
Q. As you probably heard there has been quite a bit of testimony and questions about the sentencing guidelines here as they relate to MDMA. Are you familiar with the sentencing guidelines or just generally familiar with what they are?
A. I am. I read the document that you provided and I have had previous experience with the process early on.
Q. Is that the May 2001 Sentencing Commission report regarding MDMA drug offenses?
A. That's correct.
Q. Let's go over that report which you had an opportunity to review. Have you ever, did you ever testify in front of the commission or Congress regarding this very topic, MDMA drug offenses?
A. I have testified concerning the effects of MDMA, its pharmacology and the status of the science at the time.
Q. When was this?
A. This was 2001 and 2002.
Q. There are a couple, a handful of excerpts that I am going to read almost word for word. I ask you to comment on them. On page 8 of the document, the first full paragraph, and the

third sentence of that paragraph:

A comprehensive review of the scientific literature reports findings from multiple scientific studies describing symptoms of acute toxicity from MDMA use, including mental status changes, hyperthermia, and other symptoms associated with a serotonin syndrome.

That a was long sentence, but do you agree at the time in 2001 that that was statement was true?

A. Yes.

Q. How about now; is that statement true?

A. Yes.

Q. What is a serotonin syndrome?

A. A serotonin syndrome is, as syndromes go, a constellation of effects that could be caused because of a serotonin system that is, I wouldn't say nonfunctional but it's functioning in an abnormal way. In this case it is likely because of enhanced serotonin action, and so serotonin systems throughout the body are doing things that under normal physiological conditions they wouldn't be doing and can associated with cardiovascular responses, with pulmonary responses, or with responses in the brain.

Q. Serotonin syndrome, in other words, it's not just one thing, but as you said, it's a constellation of effects on the body?

A. That's correct.

Q. Let's goes over what is in that constellation. Let's start with hyperthermia. Can you describe how MDMA relates to hyperthermia or causes hyperthermia?
A. Serotonin pathways are important in the thermal regulatory process, probably to the hypothalamus. The hypothalamus is a center of controlling autonomic systems. Autonomic systems are those that respond to environment. They help the individual body adapt to the environment.
Q. Is the hypothalamus part of the brain?
A. Yes, it is. So something that disrupts serotonin which has input into the hypothalamus, one could imagine would interfere with how the body adjusts to the environment and that would include temperature. So when we talk about hyperthermia caused by drugs like MDMA and actually the same sort of thing happens with other amphetamines as well, so it's not unique in that property. But what happens is if you are in a hot environment the body has difficulty cooling down because that thermal regulatory system has been interfered with, so the body temperature goes up, and if it's not dealt with, it can be became fatal or at least it can become pathologic.
Q. Based on your understanding of MDMA use and MDMA's physical effects on the body, why is it significant that hyperthermia is experienced in hot or elevated temperature situations?
A. I am not quite clear, why is it significant in terms of what happens to the person?

Q. Yes.
A. Well hyperthermia when it's mixed with Ecstasy or MDMA, this is a combination that results in the traditional serotonin damage that has been associated with Ecstasy use. If you don't have hyperthermia, then you don't see serotonin damage. It's pretty much that simple. In fact, in laboratory animals, if we take animals and put them in a very cold environment and we expose them to very, very high doses of serotonin, you don't get serotonin toxicity or damage. So, one would suspect that the same thing applies to humans, that is, the higher the environment, the higher the body temperature, the more sensitive the individual becomes to the effects of MDMA and its potential consequences on neurosystems.
Q. Based on your research of MDMA do you have an understanding as to whether there is a typical setting in which MDMA is used?
A. It's typically used or certainly commonly used in the rave setting or the club scene where there is lot of dancing, temperature oftentimes is elevated, and there is physical exertion and heat that's generated by all of the bodies and by the increased motion and activity of the individual.
Q. Let's move on to another effect that you testified was part of the serotonin syndrome, cardiovascular effects. What sorts of cardiovascular effects are included in this serotonin syndrome?
A. Serotonin also again through the hypothalamus and other

mechanisms can alter the sympathetic nervous system. In the case of MDMA, you not only have the serotonin piece, but you also have the norepinephrine piece which is a critical factor in sympathetic systems. For this reason you see a fairly rapid and significant increase in blood pressure, in heart rate, in pulse, the beats, number of beats per minute of the heart, and as I said, this occurs fairly quickly to a level where you would describe this person as being hypertensive if you didn't know that they had been using Ecstasy.

Q. As a result of heightened blood pressure and pulse, what kinds of ultimate cardiovascular effects have been observed?

A. They have seen arrhythmias, heart attacks, strokes that have occurred in individuals that have used Ecstasy.

Q. Are effects on the liver part of the serotonin syndrome or can they be?

A. It can be, yes.

Q. What kinds of effects have been observed on the liver in connection with serotonin syndrome?

A. There has been damage to the liver, you have what they call liver enzymes that show up when there has been damage that has occurred. These liver enzymes can go up, suggesting that some degeneration or problems have taken place in the hepatic structure.

Q. One of the items listed in the 2001 report are mental status changes. Can you elaborate on that being part of the

serotonin syndrome?
A. Serotonin we know is a major role player in emotions and in moods. Many of our antidepressant drugs base their therapeutic efficacy on the fact that they change serotonin systems. Here again it's not surprising if you have disrupted normal serotonin functions, that it may have an impact on the mood both in terms of when the serotonin comes out immediately after you take the drug and then the consequences or what we would call a withdrawal or rebound effect afterward.
Q. Another statement in the 2001 report, still on page 8, last paragraph, first sentence: The potential toxicity to serotonin neurons, however, has been the subject of some disagreement. At the time in 2001, was that true in your observation?
A. Yes.
Q. How about now?
A. The disagreement piece?
Q. Yes.
A. Yes, there is certainly some disagreement.
Q. Potential toxicity of serotonin, I will cut to the chase; we have been talking about neurotoxicity?
A. Correct.
Q. What is neurotoxicity?
A. Toxicity to neurosystems and generally we focus on the brain as being an example; there could be other neurosystems as well. My definition, I think a fairly generic definition of

toxicity implies that normal function has been compromised. If it's an acute toxicity, it has been compromised for a short period of time; if chronic, it's compromised for a long period of time.

Q. Does neurotoxicity include, as you describe it, a potential disruption in the production of serotonin?

A. That's true.

Q. Or some disruption in serotonin transporters or SERTs?

A. Yes, that would certainly be neurotoxic.

Q. Would neurotoxicity include disruption to the nervous system itself?

A. Yes.

Q. How about what we have learned throughout the hearing as axons; would neurotoxicity include effects on axons as well?

A. Yes, it would.

Q. What is an axon?

A. An axon is fiber process that comes from the cell body of the neuron or the principal braincell and it extends to its target in the brain, that's usually going to be another neuron, and it's the business end of the cell, that is, its responsibility is to make sure that the connection is to the proper place, and then when what we call neurotransmitters, these are chemical messengers that are released from the neurons. They are managed at the end of the axon, a region we call the terminal. They are managed both in terms of their

synthesis, their turnover, their release, and their reuptake.
Q. The statement itself: The potential toxicity to serotonin neurons however has been the subject of some disagreement. You testified that you believe that was true back in 2001, the date of this report, and that it's true today.
A. Correct.
Q. Could you describe the major issues in the disagreement as to potential toxicity?
A. I don't think there is any disagreement about its potential to cause neurotoxicity. That's very obvious. It happens when you administer it to animals. That happens regardless what species. Obviously you don't have studies where you are allowed to go in and administer high doses of Ecstasy and then go in and dissect the brain and do molecular analysis. We are confined to using the tools that we have that won't inflict harm or potential danger to the human and that's basically imaging. Very crude, it's getting better, but it's still very crude, and it restricts the kinds of questions we can ask about the underlying mechanisms.
The bottom line is can Ecstasy be neurotoxic. It can. It can be neurotoxic in a petri dish. If I were to just take Ecstasy and put it on top of braincells, if they were serotonin braincells, you would see a neurotoxic effect. It's even neurotoxic if I were to put it directly onto tryptophan hydroxylase which is an enzyme that synthesizes serotonin, it

will decrease that activity and it will do it very rapidly. And it does these things through an oxidating process. It turns out that the amphetamines in general and Ecstasy in particular has the potential to generate reactive oxygen species.

Q. What is a reactive oxygen species?

A. It's a molecule that is looking for an electron or it is oxidizing its targets and so what it does is it disrupts normal molecular functioning, it can interfere with energy production, it can damage DNA, genetic material. So if it's not controlled and if it happens at a level that's too intense, it can certainly compromise a cell's function or even in the extreme, kill the cell.

Q. You testified earlier that neurotoxicity includes not just disruption of serotonin, serotonin transporters, but disruptions to the cell itself as well as the axon?

A. Correct.

Q. Has it been substantiated or at least suggested that MDMA has an effect on the axon, the actual neuron?

A. The implication comes from evaluating the protein SERT or serotonin transporter. As I said, it's a fairly crude way of doing the analysis but at this point it's about the only way we have. This transporter protein is only found in serotonin neurons. So if the amount of the protein goes up or if it goes down, we assume that changes have taken place inside of the

neuron, and we make an assumption that if it goes down, that we have lost pieces of that braincell. I guess if it went up, you would assume that we have gained pieces.

So it's a very simplistic analysis of quantitative changes in that protein. We use that as our way of assessing in live people whether their serotonin systems have been changed.

Q. Give some examples of studies, preferably recent studies, that have set forth that indication that you just described that because of fluctuation in serotonin transporters, there is a suggestion or an assumption that damage to the axons has been done?

A. The more recent studies, they have been talked about considerably up to now, is the Stephen Kish study where he looked at, we call it a ligand, it's a molecule that selectively binds to that SERT protein, and he observed in low to moderate Ecstasy users that there were decreases in this transporter in brain regions, the hippocampus and in some cortical regions.

Q. Any other studies you can think of at this moment?

A. Well, there are a bunch of McCann studies which we talked about. That group continues to do research and continues to show those same kinds of changes. So there have been a number of individuals who found that there are these shifts in the transporter levels using brain imaging, path and SPECT imaging.

Q. You are aware of the Netherlands NextC study?
A. Yes.
Q. You are familiar with a couple of the authors or participants in that research?
A. The de Win, yes.
Q. Have you reviewed papers that have come out of the NextC study?
A. Yes, I have.
Q. Have any of those papers spoken to this topic you just described?
A. They have and they actually used some other strategies, imaging strategies. They used MRS, magnetic resonance spectroscopy. This is an imaging technique that looks at other measures, more generic measures, not selective serotonin measures, but they were interested in a measure of glial or non-neuronal cell function. They were interested in also blood flow, volume of blood flow where blood was going, and they were interested in looking at measures of what we call light matter. That would reflect myelin or non-neuronal or glial cells as well. Then they did, they also did a SERT ligand with the serotonin transporter.
Q. Is that similar to what happened in the Kish study?
A. It's a different ligand. It's been an issue of how selective these ligands are, do they only bind to the serotonin or do they bind to other targets or what is the background

noise. Some of these earlier ligands were fairly noisy, so it was hard to pick out what was selective binding and what was just nonspecific binding.

Q. To be clear, a ligand is basically a tool for researchers that will show, that will attach to serotonin transporter chemicals?

A. Correct. Then the ligand has a radioactive emitter so that you can pick it up on your imaging technology and you can see where it is so you get a single vision of intensity that has an anatomical component to it so you can see where and quantify.

Q. Another statement in the 2001 report, page 9, the first full paragraph, second sentence, this is an observation from one particular research study: The brain scan comparison of MDMA users with nonusers indicated that users had a significantly reduced number of serotonin transporters throughout the brain and that the magnitude of the loss was associated with greater use of the drug.

That's a statement in 2001?

A. Correct.

Q. Are you aware of studies that came to this particular observation back in 2001?

A. Probably mostly based on the McCann studies.

Q. How about today, have there been studies that have observed these particular phenomena?

A. Again, I think they have been cited. There tends to be

this dose response phenomenon, that is, the heavy users, the more intense the history of using Ecstasy, the greater the likelihood of seeing these markers change, and one would suspect that the longer the duration of the change, whether it's permanent or not, but those discussions are still being had.

Q. You predicted the next excerpt in the 2001 report, page 10, first full paragraph, first sentence: Another point of controversy surrounding the MDMA research literature is whether loss of these serotonin sites and corresponding impairment is permanent.

Back in 2001, I know you have had a chance to read this 2001 report, did that point of controversy actually exist?

A. It did.

Q. How about now?

A. It still exists.

Q. Describe just the nature of the controversy; what are people talking about here?

A. Well, in some cases they are comparing apples and oranges, so on one hand there is the discussion about the recreational use and almost by definition that means low dose, 1 to 2 tablet kind of use where you are getting maybe 1, 1-1/2 milligrams per kilogram of the drug versus intense use where somebody maybe is taking 4, 5 tablets, getting up to around 5 milligrams per kilogram of the drug.

And those two groups may present in very different ways and it's going to be a sliding scale. It's not going to be black and white. You are going to find a lot of gray between those extremes and that gray is going to vary on a number of principles, for example, the environment. I already mentioned that whether there is damage or not depends a lot on how high the body temperature goes.

That's going to be dependent on the environment, whether it's an environment that's got an air conditioner and all the windows are open and you are in the mountains and there is a cool breeze or whether you are in downtown New York in the middle of the summer and the air conditioner is gone. So that's going to change.

(Continued on next page)

A. So that is going to change and then it is also going to change also based on other factors like are there other drugs in the body, is the individual bringing other vulnerabilities to the issue or the experience.

We are not talking about genetics, and genetics have not really been studied relative to MDMA very much, but it certainly has relative to methamphetamine toxicity, and genetics seems to play an important role. And my guess is that it is playing that role here.

So there are a lot of variables that are happening. And at the end of the day, you get a group of people who are low users and you don't see a significant change. And you say the drug seems to be not particularly dangerous.

And somebody else gets another group, just as legitimate research, but all of these other potentiating factors are in place and they see a change and they say, look, it has the potential for causing some significant damage.

Q. Now, the point of controversy here is identified in that sentence was, whether the loss of the serotonin sites, the neurotoxicity and the impairments were permanent.

At the time of the 2001 report, was there evidence or was evidence offered that neurotoxicity and those impairments were temporary?

A. I would say more could be permanent or could be temporary, again, based on what your subjects look like.

At the time we had somewhat limited -- I shouldn't say limited -- we had been looking at the drug for almost 15 years in this country, but still is 15 years permanent? Is 20 years permanent? It depends how long you live as to what permanent is and how permanent is defined.

The implication, the data that was present suggested that it was going to be long lasting in some users. Whether you call that permanent or not, it certainly seemed to be a possibility for some people.

Q. But is it fair to say that there were studies or data at the time in 2001 that in certain relatively lower dosages, the effect of the neurotoxicity and the impairment was not long lasting?

A. Yes. There was discussion on both sides. There was discussion, look at some, it seems to be long and even profound and in others it seemed to be minimal and temporary.

Q. I am going to go back in this report to page 8, last paragraph, second sentence: A leading researcher in MDMA toxicity studies and the focus of some of the controversy has performed numerous studies on both animals and humans and, again, I will cut to the chase. That researcher is George Ricaurte.

Do you know George Ricaurte?

A. I do know Dr. Ricaurte.

Q. And do you know that the Sentencing Commission did consider

his research in deliberating over the sentencing guidelines?
A. Yes, they did.
Q. Are you aware of a study or a publication by Dr. Ricaurte and his research team entitled "Severe Dopaminergic Neurotoxicity in Primates after a Common Recreational Dose Regimen of MDMA," published in Science in 2002?
A. I am.
Q. Have you reviewed that particular publication?
A. I have certainly read it in some detail.
Q. Were you acting director of NIDA at the time that that publication was issued?
A. I was.
Q. Are you aware that that publication was retracted?
A. Yes, I am.
Q. When you first read the publication -- actually, was it in published form when you first read it?
A. I may have seen a preprint of it. I can't remember, but it was soon after it was published if not just before.
Q. What was your reaction to it?
A. It did not correspond with my experience researching this drug.
Q. Can you just tell us generally what the article and publication was about?
A. Well, it talked about Ecstasy also being a dopamine toxin and this comes from the fact that methamphetamine which is

chemically related. MDMA stands for methylenedioxymethamphetamine. So it is a methamphetamine analog.

Methamphetamine damages both serotonin and dopamine, so Dr. Ricaurte was reporting that in his research he was seeing some dopamine damage along with the serotonin damage.

And we had looked at this a number of times and had never seen any hint of dopamine damage. Others such as Bryan Yamamoto had also looked at it several times and had never seen any damage to the dopamine system.

So I was -- let's say healthy skepticism was my reaction to it.

Q. Now, you had a chance to review the 2001 report. Is neurotoxicity to dopamine or its related processes mentioned anywhere in the 2001 report?

A. No.

Q. But you did testify, is it true, though, that MDMA use has an effect on dopamine?

A. It is.

Q. Can you describe that effect?

A. MDMA is what we call a releasor molecule in contrast to serotonin selective uptake blockers which are uptake block inhibitors. Cocaine is an uptake block inhibitors. The amphetamines are releasors, so their mechanism is very different.

Both kinds of drugs will result in an increase of the transmitter serotonin and dopamine. Increase in those transmitters outside of the cell and the message that they send will be augmented, but they do it in very unique mechanisms.

With MDMA, what it does is, it disrupts the storage of the serotonin inside of the cell. The serotonin is stored in little packages we call vesicles. And these vesicles have proteins on them called vesicular monoamine transporters.

And these transporters take the serotonin, once it is produced, and put it inside the vesicles. And this is done for two reasons. One is that it prepares it so that if that brain cell is stimulated, the vesicle will then traffic to the terminal and dump out the serotonin and the serotonin can exert its effect.

But also it does it because serotonin has the potential of becoming an oxidative problem for the system. So by packaging it and keeping it inside, you sort of protect it and prevent it from doing this molecular explosion.

Q. Does MDMA have the same type of mechanical effect on dopamine or is it different?

A. Both of them, it does it to dopamine and it does it to serotonin.

Q. You described to us in the context of serotonin syndrome how that release of serotonin affects various bodily systems. How does the release of dopamine affect various bodily systems,

if at all?
A. It does. It is important to keep in mind that the relationship between the two exists, that is, that the MDMA causes about 10 times more serotonin to come up than it does dopamine.

So a comparison to methamphetamine, methamphetamine is more of a one per one. That is why Ecstasy is more selective to the serotonin system, whereas methamphetamine hits both dopamine and serotonin. So Ecstasy does cause the dopamine to come out.
Q. What happens when the dopamine comes out?
A. It activates its receptor targets. This is probably the basis for some of the euphorigenic properties of the drug -- the stimulation, the energy, the enthusiasm. And it also tends to be the basis for the addiction process for drugs of abuse in general.
Q. As you probably heard by now, addiction is a hot button issue here?
A. Yes.
Q. You testified that dopamine is related to the addiction properties of drugs?
A. Correct.
Q. Does the MDMA effect on the dopamine system have any relationship with the addictive properties of MDMA, if those addictive properties exist?

A. It would. It is confounded by the issue that there is this disproportionate amount of serotonin that is coming out. And what it looks like, the serotonin may get in the way of that normal addiction.

So when you heard some equivocation on the part of Dr. Parrott, well, it is not addicting as, say, cocaine or some of those other stimulants of abuse -- at least not at the onset it doesn't appear to be. But as the person continues to use it over extended periods of time, especially if they start escalating in dosages, then the addiction key start to show up more and more.

And we think what is going on is, this reflects a loss of some of the serotonin influence because the serotonin seems to trump the dopamine when it is so disproportionate. But as you lose some of that serotonin action, then the dopamine effect becomes more dominant. And at that point the drug experience is likely or more likely to go on to become an addictive exercise.

Q. Just to be clear, is your testimony or your observation that, upon initial use of MDMA, the serotonin release is proportionally larger, as you say, 10 times larger than the dopamine release, correct?

A. Correct.

Q. And the dopamine release, typically, for drugs, is related to the addictive properties of the drugs?

A. Yes, that's true.
Q. Because in the beginning with the initial use of the drug, the serotonin release is greater than the dopamine release, you don't see necessarily an addictive property to the drug, correct?
A. Right. Certainly it is minimized.
Q. So let's stop there. You went on to describe a second step in the serotonin, the effect on serotonin in the drug. What is that second step?
A. Well, you mean in terms of, as the serotonin influence starts to deteriorate and the dopamine influence starts to increase?
Q. Exactly.
A. So that brings with it -- that is associated with the reward pathways, what we call the mesolimbic pathways. And these are almost always involved in energizing that addictive process, where the person is inclined to do it over and over and over again.
And then you start to get some subtle changes in the dopamine system that can take you into a very compulsive behavior. And you use the drug and sort of the general definition of addiction is that you are so compulsive about using the drug that you disregard all the negative consequences that are resulting.
And this is an extreme position of addiction for

someone that has Ecstasy. It happens. Certainly doesn't happen as often as with cocaine or, say, with the heroin, but it happens as Dr. Parrott was mentioning.

Q. Are there any other features -- there has been a lot of comparison between cocaine and MDMA, especially with respect to addiction. Are there any features of cocaine use versus MDMA use that may also contribute to the differences in the addiction properties?

A. Well, the cocaine, it doesn't have that disproportionate piece between the serotonin and the dopamine influences. They are more of a one-to-one relationship, and they may even be more on the dopamine side than on the serotonin side.

So you don't have to suppress the serotonin in order to allow the dopamine effect to express itself. It is going to be there. It is going to be there from the first exposure to the drug.

Q. Is there anything about how these respective drugs are used or administered that relates to the addiction properties of the drug?

A. What we call the pharmacokinetics, and this has to do with how a drug is administered, how it distributes, where it goes once it gets inside of the body, how it is metabolized and how it is eliminated.

Those are different for these two drugs. The Ecstasy is typically taken orally. And, usually, an oral drug is less

likely to be addicting than if you took that drug and you injected it IV or if you smoked it.

Q. Why is that?

A. It has to do with how quickly the drug gets into the brain and how much of it gets into the brain at one time. If you are smoking, say, like crack cocaine or you are IV-injecting crack cocaine, it gets into the brain in a matter of seconds. When it hits the brain, it hits it in a very high concentration, so the effect on the dopamine system is abrupt and it is fairly dramatic.

With Ecstasy you are taking it orally. It goes into the gut. It has to diffuse across the lining of the gut, and the intestines, gets into the bloodstream goes into the liver. Some of it gets metabolized, makes it way up to the heart.

Eventually it gets up to the brain. And when it gets there, generally, the concentrations of the drug will be diminished, so it doesn't hit the brain in this one bolus like you would see with cocaine.

Q. Do you know whether Ecstasy is consumed in ways other than just an oral administration?

A. An oral administration is by far the most common use. Occasionally you hear of people who try to snort it, and I am sure that there are people who inject it intravenously, but that is fairly unusual.

Q. You have had a chance to review a document dated November

22, 2010 that contains, in essence, summaries of proposed testimony by the defense's experts, correct?
A. Yes.
Q. Dr. Curran and Dr. Halpern?
A. Yes.
Q. I want to read a handful of excerpts, and I would like to ask you for your reactions and general comments.
A. OK.
Q. We will start with Dr. Curran's proposed testimony or a summary. "Many of the early studies in MDMA failed to account for confounding variables such as polydrug use, psychological history and biased self-reporting." Was that true back in 2001 with those early MDMA studies?
A. They probably didn't ask those questions very much then, and they are asking them now. So in terms of attitude, one could say yes, that's a little different.
Q. Polydrug use, a confounding factor that has been discussed during this hearing. Can you comment on the significance of polydrug use in the study of MDMA?
A. It is known that the vast majority of MDMA users are polysubstance abusers. And so I guess I find it interesting that we are so concerned about what does MDMA do all by itself when in fact, in reality, that's not going to be very practical.
In reality, the vast majority of the users are going

to have these other drugs on board, so probably a more relevant real time question is, what does Ecstasy do when these other drugs are on board. So I think that that's a factor, but there have been some studies that have been done that have tried to sort that out.

Does Ecstasy really bring some potential problems in that sort of an environment?

Here, again, the answers have been somewhat equivocal. There have been those who have said no. When we factor out the polydrug use, the Ecstasy, the common theme that seems to be present in all of these is causing an effect.

And then other studies have said, well, when we factor out the polydrug use -- or the polydrug use itself seems to be causing some of these effects. So that minimizes the contribution of the Ecstasy.

Q. How about psychological history as a confounding factor in these studies? What is the significance of the preexisting psychiatric conditions in MDMA users?

A. Here, again, this is a very critical real life issue that has to be addressed because it is true that a lot of these people bring with them psychological baggage.

And here, again, I find it somewhat interesting that as investigators we lean over backwards to make sure that we clean up our sample and get rid of all of the underlying psychiatric issues. Those are exclusionary criteria. If you

have depression or you have some significant psychological history, we don't want you to participate in this. When in reality, these are the people that are using the drug and exposing the drug.

And one would suspect that the interaction between the pharmacology of the Ecstasy and the underlying pathology of the psychiatric disorder are probably going to interact and create problems for these people.

Q. Another sentence or another excerpt from the summary: "According to the best recent studies of the effects of MDMA in humans, the drug's effects are relatively mild and not permanent." What is your reaction to that?

A. Well, I guess the definition of "mild" is in the eye of the beholder. I had to smile when we had the discussion about you forget 1/30th of these names or words. Well, what if you are at the party and there are 30 people there and the name that you forget is your boss? That becomes pretty critical.

So if you are not always selective as to which are the 1/30th of the words you get to forget nor are you able to select when you forget them, so any compromise of your ability, whether you call it subtle or dramatic, can be pathologic, can prevent you from getting that raise, can make you less competitive in a very competitive world.

So for one person that is a farmer and not talking to anybody, in a very simplistic world, maybe you can get by with

that and it is not going to change your life. But if someone is trying to function in the corporate world of downtown New York, that can be a very critical issue.

I struggle a little bit with, a little bit of deficit isn't a big deal and we should be happy with that, but I am not sure that we should ever be happy with losing function.

Q. Well, your reaction to that statement was in terms of function, right, not memory losses, name or other things in real life?

A. Right.

Q. And I think this is your area of expertise. What about the biological effects? Do you agree with the statement that, as it applies to biological effects, that the effects of MDMA are relatively mild biologically?

A. Well it comes back to the issue of how do you define "minor," how close are you to the edge and how far do you have to be pushed before you go over the edge. If you are biologically a long ways from the pathologic edge, yeah, you can afford to be pushed a little bit towards it. But if you are right on the edge and you go over --

Let me just give you an example. A lot of the discussion I have heard today, I have heard before relative to methamphetamine. We had some of the same discussions about methamphetamine back in the '70s and the early '80s for some of the same reasons, methodological reasons. And we found that we

were one of the first groups to find that there is this dopamine deficiency that occurs in laboratory animals, and it took almost to the latter part of the '90s to confirm that in humans.

And then the question is, you only see like a 10 or 20 percent deficit in the dopamine system in humans, how big of a deal can that be?

Well, we just found with a study that is going to be published that it is big enough that we are finding those who have a history of methamphetamine dependence are five times more likely to become Parkinsonian patients.

So it is only a 10 or a 15 percent push down a road that leads to degenerative pathology that shows up later on in your life. So 10 percent when you are 30 doesn't seem like much, but 10 percent when you are 60 and you are close to the edge of Parkinson's, all of a sudden, that becomes very critical.

So those are questions that are out there that we haven't answered, but we have to consider.

Q. Next statement: The drug does result in impairment of human user's verbal memory, but the drug's effects wear off over time and deficits in brain chemistry do not persist.

Your reaction?

A. We have to keep in mind that, at least in the human studies, we are using very crude methodology. All it tells us

is, there are changes in the quantity and some of the anatomical, but very crudely, the anatomical distribution of that protein in the brain. That's all we can tell from our imaging strategies.

Q. Has there been conclusive evidence that deficits in brain chemistry do not persist?

A. I think there have been studies that say no, it doesn't or that there is some recovery that occurs.

Q. Has there been conclusive evidence that full recovery occurs from any dosage of MDMA?

A. That is a question that we can't answer yet, quite honestly. We don't have the methodology in humans to answer that question. So we can say, yes, it looks like on our scans that the serotonin transporter levels come back to normal or a normal range -- because you are always dealing with a range. Does it come back to a normal range? And using the fairly simplistic cognitive assessments that we typically use that the function returns, we can say, yes, that happens.

But what we can't say is, we can't say does quantity of the serotonin transporter mean that normal function has totally returned? And normal function really reflects on how do you survive in a very complex world.

And our assessments and our tests, usually they are done in a very sterile environment. We put them a room. We keep everything quiet, and we try to focus in and dissect out

various pieces of cognition. But cognition doesn't exist in isolation.

Maybe a better strategy would be to take them to work and evaluate them under the various complexes of work and pressures and demands on their time and how do you interact with your family. And you look at the complex day-to-day living issues and ask those questions, and those questions have not been answered. They have not been asked.

Q. Let's move on to Dr. Halpern's section of this.

There is a statement in here that recent prospective studies on humans have not found significant changes in serotonin systems over time or evidence of permanent damage. Do you agree with that statement?

A. Again, I think Dr. Parrott gave several examples of studies that have shown that there are changes and those changes persist for months. There are studies out there that say that they persist for 10 years now.

Q. "Unlike cocaine, MDMA is not addictive." Do you agree with that?

A. Well, we talked a little bit about addictive in a different way. The mechanisms are different because of this very prominent upfront serotonin piece that we see with Ecstasy.

Q. So do you agree with that or not?

A. I would certainly say it is less addictive in initial exposure to the drug, yes.

Q. But you testified earlier about how it becomes addictive?
A. To those that escalate their doses, yes.
Q. "Unlike cocaine, MDMA does not induce a breakdown of the blood/brain barrier." Do you agree with that?
A. No. Most of your sympathomimetics will change your blood/brain barrier. There have actually been a couple of studies that have looked at MDMA, and it says it works pretty much like other sympathomimetics, and it will break that blood/brain barrier down.
Q. What is the significance of a breakdown of a blood/brain barrier?
A. Well, the blood/brain barrier is supposed to be protecting the brain from large molecules or from things that could damage or interfere with the normal functioning of the brain. So if you were to break that down -- let's say metabolic products that are part of normal living. Well, they are not supposed to get in the break because they muck up the system. So if you break down the brain and these things start to get into the brain, then they can interfere with how the brain works, and it can cause things such as confusion or some of the mental issues that we see associated with some of these drugs.
Q. There have been questions asked about relative harmfulness of cocaine and MDMA. Can you state whether one drug is more harmful than the other?
A. I won't state it again in the generic way, but if you

became specific, that is, if you looked at the acute toxicity on cardiovascular systems, how does that compare, you could make a comparison.

We already talked about addiction. Cocaine upfront is going to be more addicting than Ecstasy is.

Both of them, as sympathomimetics, can cause problems with the cardiovascular system. They cause death.

There are individuals who have evaluated that and have claimed that they are fairly similar in that property because both of them enhance norepinephrine systems in quantitatively similar ways, so arrhythmias, heart attacks, strokes -- those kinds of things you would see somewhat equally between the two drugs.

If you started to look at what we call cellular neurotoxicity, cocaine tends not to be very neurotoxic to the cells whereas, as I have already mentioned, Ecstasy itself, the MDMA itself creates these oxidative events that are problematic for the cell, and cocaine doesn't do that. And it goes back to its basic mechanism whereas cocaine is an uptake blocker, its functions are a lot like the serotonin selective uptake blockers -- in fact they compete for the same site on the protein in the serotonin system -- whereas Ecstasy, it goes right into the cell. It alters the vesicle storage. And it creates this problem for the cell in terms of how do we deal with his reactive oxygen species.

Q. Is it fair to say that cocaine and MDMA share certain harms?
A. They do.
Q. And is it fair to say that cocaine has certain harms that MDMA doesn't?
A. Yes.
Q. Is it fair to say that MDMA has certain harms that cocaine doesn't have?
A. That's correct.
Q. Along the lines that you just detailed?
A. Yes. And I talked a little about tryptophan hydroxylase. Cocaine doesn't do anything to tryptophan hydroxylase, whereas you will see this fairly significant depression of this enzyme over days. Usually it will come back, although in some cases it stays down for longer periods of time.
Q. Just to be clear, that depletion of tryptophan has an effect on serotonin production?
A. It does. Tryptophan hydroxylase is the enzyme that synthesizes serotonin. So if your tryptophan hydroxylase isn't functioning, then your stores of serotonin goes down and they will stay down until you are able to replenish that enzyme and restore its function.
Q. Based on your reading of the 2001 MDMA, the Sentencing Commission report, were there any harms that the commission forecast with respect to MDMA? Did it predict any harms?

A. Well, I am not sure that it predicted specific harms other than to say, generically, we need to be cautious. We are concerned that there are trends here, and we need to be paying attention to these trends as to the persistent effects of Ecstasy in some users.
Q. Dr. Halpern has an excerpt in his summary: "Year after year, studies of MDMA users failed to replicate the harms forecast in 2001." Do you agree with that statement?
A. I am not sure what he is referring to.
Q. Like what?
A. As I said, I don't see that there were harms that they predicted. I didn't ever read in that that there is this epidemic of people who had total wipeout in their serotonin systems and fill their psychiatric institutions -- there isn't any kind of dire predictions like that at the commission.
Q. There is this ultimate statement from both Curran and Halpern: "Today, no reasonable scientist aware of the intervening scientific literature since 2001 could arrive at the same conclusions espoused by the 2001 report." Do you agree with that?
A. No, I don't -- well, I would hope that is not true because that's kind of where I am. So I hope I am a reasonable scientist.
Q. Are you the only one where you're at?
A. Well, I would say that most of the basic scientists that

work in this area would agree with me. Those of us who are familiar with this molecule and how it works would still say, this is a troubling molecule, and when it is released, especially used by young people without any kind of discretion or any kind of control -- and young people are attracted to use this and, unfortunately, a lot of them think it is a fairly innocuous molecule. We see potential problems with that kind of a backdrop.

MR. CHUNG: No further questions at this time.

THE COURT: We will take a very short recess.

Dr. Hanson, will you step down for a few minutes.

We will reconvene in 10 minutes.

(Recess)

THE COURT: Cross-examination, Mr. Rorty.

CROSS-EXAMINATION

BY MR. RORTY:

Q. Good afternoon, Mr. Hanson.

We have talked over the last two days and you just did in your direct testimony about the United States Sentencing Commission 2001 report and its comparison of the harms of cocaine and MDMA?

A. Yes.

Q. As you know, the commission believed at that time that MDMA was more harmful than powdered cocaine, correct?

A. Yes. I would say that they inferred that, sure.

Q. That was the commission's conclusion?
A. Right.
Q. And based on your reading of it, part of the basis for the establishment of criminal penalties for MDMA?
A. Correct.
Q. What I understand from your testimony is that, as a scientist, that comparison is, to some extent, apples and oranges because there are different kinds of harms?
A. Right.
Q. In attempting to answer this question that interests lawyers and judges about which is more harmful and how they should be ranked, you simply approached that from a different angle as a scientist?
A. That's correct, yes.
Q. That's because, first of all, they are different types of drugs?
A. Correct.
Q. They have different effects?
A. Right.
Q. They have different harms?
A. Correct.
Q. So as a scientist, if you yourself set out to study harms, you would be more interested in narrowly examining the psychopharmacological effects of a drug than you would be to the more simplistic task of saying, which of these two

substances is more harmful?
A. Right.
Q. Let's turn to neurotoxicity and its meaning and relevance.
Am I correct that since 2001, you and your colleagues in this field are better technologically equipped to study neurotoxicity?
A. In humans?
Q. Yes.
A. I would say that that's true to a certain extent. As I mentioned, the tools we have are still somewhat limited and they are ambiguous because we can only look so far into underlying structure and function. But we are certainly further along than we were in 2001.
Q. To take one example, perhaps the most important one for our consideration, there have been advances in neuroimaging?
A. Correct.
Q. Since 2001?
A. Right.
Q. And those are reflected in the differences between the McCann study and the Kish study, is that correct?
A. Yes. Dr. Kish, as he describes in his paper, he is more selective than had been before.
Q. So it is fair to say simply that the techniques are more developed and neuroimaging tells us more and better than it did before?

A. It gives more precision than what we had before.
Q. As a result, more information and probably more accurate information?
A. True.
Q. Staying with neurotoxicity and its definition, you describe neurotoxicity as compromising normal function?
A. Correct.
Q. When a person's serotonin is decreased, you would say that their normal function is compromised, correct?
A. Correct.
Q. That is the normal function of serotonin?
A. Of serotonin and anything that serotonin is influencing, so you have a cascade of effects.
Q. When you talk about compromise and function there, you are talking about brain change as opposed to functional impairment in behavior?
A. But they are connected.
Q. There may be a correlation, but when you use that term, that is, neurotoxicity and the depletion of serotonin, what you are describing is a brain change?
A. But I would say, being a neurobiology type, I would say that any behavior reflects neurochemistry, so you have changes in neurochemistry. There are going to be changes in behavior that will eventually be expressed. Whether you use the correct test to pull that behavioral change out is always an issue of

discussion, but that's going to be the link. If you change chemistry, eventually down the road you are going to impact behavior in one way or another.

Q. But not all brain changes, for example, serotonin depletion, have a direct correlation to functional impairment in a person's behavior?

A. I think that they probably do if you were able to do the right kinds of tests.

Q. Part of what we have been talking about here is whether or not the field has done those kinds of tests?

A. And we may not be there. Our testing may be very crude, and we still may not be asking all of the right questions. And that's another piece that has changed a little bit from 2001 to now is that the way we are asking the questions is changing a little bit, but we are still getting the same answers, that is, they are equivocal answers.

We are seeing changes sometimes and sometimes we are not seeing the changes.

Q. In discussing neurotoxicity or the compromise of normal function, there is a difference between acute compromise, that is, immediate time-sensitive compromise and chronic compromise or long-term compromise, correct?

A. Correct.

Q. You would draw that distinction and you can draw that distinction in studies and tell pretty clearly what the

researchers have looked at, acute or chronic?
A. I would say that your point is correct, but there is a continuum. There is a point where acute becomes chronic and chronic becomes permanent. And it is not always easy to draw a line and say, OK, you are done with the acute stuff. Now we will look at the chronic stuff, because sometimes they just melt into each other.
Q. But in evaluating a study, it is important to know and ask questions about that study, when the evaluation took place in relation to ingestion of the drug?
A. Correct.
Q. How much time has passed?
A. Yes.
Q. What other factors are involved?
A. Depending on the questions you are asking, but yes.
Q. All disruption in serotonin production is not necessarily chronic, correct?
A. I think that that would be true.
Q. There is no disagreement that MDMA has the potential to cause neurotoxicity, that is, compromise of normal function in its acute status, that it has the potential to cause immediate compromise, say, of serotonin levels?
A. Right.
Q. That is an area of agreement?
A. Yes. I would hope so, yes.

Q. But I took from your testimony that there is not an agreement with respect to chronic compromise of normal function?
A. Right. And if there is chronic compromise in the system, what does that mean functionally, so it is a related but different question.
Q. And that is a lot of what we have been talking about here today?
A. Correct.
Q. I am trying to narrow down the area of disagreement.
A. Correct.
Q. And what I understand from you is, there's pretty good agreement that there is acute disruption of normal function?
A. Right.
Q. There is not agreement that there's chronic disruption of normal function?
A. I think that most people would say that there is the potential for chronic disruption, but maybe the discussion is how relevant is that potential to the real life, real world situation.
Q. This distinction that we have just been discussing, acute versus chronic, that was not a distinction that the commission focused on in 2001, was it?
A. They didn't say it explicitly, but they implied it, that is, they did talk about the immediate effects on cardiovascular

systems on emergencies and that sort of stuff. So that would be acute toxicity. And they talked about more persistent effects and that would be chronic toxicity. So they didn't use that terminology, but I think they referred to the principles.
Q. In their summary of harms, they didn't make specific reference to chronic impact?
A. I don't remember the exact enumerated things that they included in their summary of harms, so I cannot say whether they referred to chronic or acute.
Q. Let me refresh your recollection in a moment.
A. OK.
Q. Let's move back to our discussion of neuroimaging and the effect of advances in the field.
A. OK.
Q. You identified the distinction between the McCann and Kish neuroimaging studies, correct --
A. Right.
Q. -- and particularly the ways in which the Kish study benefitted from those advances?
A. Right.
Q. Dr. McCann's study concluded and the commission relied on that there were chronic effects, chronic problems with SERT binding based on neuroimaging?
A. Right.
Q. Yet the Kish study concluded -- did not come to that

conclusion?
A. Well, the studies were designed differently and the subjects were different in terms of their Ecstasy experience.

(Continued on next page)

BY MR. RORTY:
Q. Let me refer you to one quote from there.
A. This is the Kish study.
Q. Yes. We did not find a global massive reduction of brain SERT finding as reported in the first SERT imaging studies of Ecstasy users. Then there is a citation to McCann.
A. Correct.
Q. So Kish did come to a different conclusion than McCann although the studies may have had some differences in methodology, Kish felt it was important to relate back and to refer to McCann?
A. He does equivocate saying there is a distinction between the intensity of use of subjects in the McCann versus ours and he saw some tendency, I think he mentions that one or two of his more intense users, they did appear to have some SERT changes in the caudate or in the striatum. So I think he distinguished the differences between his study and the McCann study.
Q. He actually illustrates another important point I want to ask you about. I took from your testimony that with respect to chronic damage there is a significant difference between low to moderate users and heavy users?
A. Correct.
Q. Am I correct that that awareness, that distinction between low to moderate users and heavy users has been refined since

2001?
A. Maybe refined but the basic principles have not changed. We have known that for a long time. In fact, one of the interesting things with the Kish study, I know Dr. Kish very well, we have collaborated on a couple of studies in fact. He called me about this study when they had completed it and he asked me about the interpretation of the data. And he says, so, does this go against what you guys have seen in the animal studies. I said no, it's exactly what we have seen in the animal studies, and that is the hippocampus and the cortical structures are more sensitive to lower doses of MDMA than is the caudate and the striatum.

so what I think he's got, he is looking at this lower dose effect that those systems are sensitive to it, whereas the caudate effects are not showing up and they don't show up until you increase the doses

Q. The lower dose effect relates to what we understand to be average recreational use in human beings?
A. Right. It would be more consistent with a typical recreational Ecstasy user.
Q. You say we have known this for a long time. To a layperson we have called this by a lot of names, but even to a layperson, a person takes a small amount of drugs, they expect less harm, a person takes a lots of drugs, they expect more harm?
A. That's pharmacology. Ecstasy does not violate the basic

principles of pharmacology.
Q. Yet the commission's study, the 2001 report, did not itself distinguish between low to moderate users and heavy users, did it?
A. Well, I think what the commission was doing, unbeknownst to themselves, was they were actually talking about what we call benefit risk in the pharmacology world, and in this case the benefit would be defined by the recreational users. They get some recreational benefit from it, and how high do you have to push the dose before you start to get some serious consequences. And we do that whether the drug has been FDA-approved or it has not been, it really doesn't matter to the drug. But if there is a wide range, if there is a big difference between the desired effect and the undesired effect, then we consider it a good drug; if there is not much of a range, then it's a bad drug and it gets us into trouble.
Q. Like cocaine?
A. Like cocaine and like Ecstasy, because Ecstasy, the drug range already with recreational changes, we are sighing from the Kish paper that you are getting some SERT changes in pretty critical brain systems, in hippocampus and in cortical regions, and my guess is if, I can't remember the explicit doses that his high dose users were using, but if you get up to the 5 milligrams, this is certainly what we see in animals, we start to see some of the SERT changes in the caudate. All you have

to do is double or triple the dose and the effect is starting expand and starting to hit other serotonin systems. That would be a concern if it were a prescription drug and certainly a concern in a recreational drug.

Q. In usage rates by heavy users at significantly greater use rates than the average recreational user?

A. I think that's probably true.

Q. To highlight that, another quote from Kish: Nevertheless, most Ecstasy users have few cognitive complaints after the acute effects and the drug withdrawal phase has passed and user values generally fell within the normal control range?

A. I would say that's true; most of them once they get to that acute toxicity stage, then you probably don't hear a lot of discussion about it.

Q. Because we have now established a distinction, the impact of dosage rates between low to moderate users and heavy users, that moves us to a discussion of dosage. I am going to ask you some questions about your own work and dosage rates. Your own experiments have been entirely in animal systems?

A. That's true.

Q. You have not done an MDMA animal study since 2005?

A. Actually we have; we have not published. We always throw in MDMA for comparison to other drugs because it has a unique pharmacology profile that helps to elucidate mechanisms, but we have not published.

Q. Your pre 2005 research on MDMA were animal studies?
A. Correct.
Q. Am I correct that you usually use 10 milligrams per kilogram or more of MDMA as your dosage unit in your previous animal studies?
A. That's correct, although as I have said we will find effects with 5, but when you are doing research like that, you want a very robust effect. So you kind of find a dose that's not going to be lethal. 10 never kills any animals and doesn't cause seizures. The animals do quite nicely. They survive 10 without any problems. We get changes are like 50, 60, 70 percent changes. We can start to tease mechanisms apart.
Q. You increase the dosage to achieve a more robust effect?
A. Correct. In effect, we can see at half that dose, but you are talking more like 20 and 30 percent changes versus 50 to 70 percent.
Q. If you were to undertake animal studies now would you use the same dosage?
A. Yes. Let me equivocate a little bit. One thing that has not been done, and Michael Baumann is one of the nice papers that is starting to look at this. That is, to look at the 1 to 2 milligram per kilogram range, and Dr. Baumann says that he's done this excercise that tries to equate doses and he finds that the doses equate pretty well across species. So 1 to 2 milligrams per kilograms in a rat give effects that are

probably fairly similar to 1 to 2 milligrams per kilogram in humans.

He doesn't see the serotonin transport decreases. I have talked with Michael ad nauseam about this issue. But what he does see, he does see some functional changes, and he says, well, since we don't see serotonin decreases, serotonin transport decreases, we don't call that neurotoxicity. My response is, but, Dr. Baumann, if you are getting persistent functional changes, then how can you not call it toxicity when the definition of toxicity is you interfere with normal functioning. So he went, well, it just depends on how you define the word.

Q. You said a number of things about Dr. Baumann's work. It sounds like you understand and to some degree accept his interest in the effect of a lower dose?

A. Correct.

Q. So that 1 to 2 milligrams per kilogram is a perfectly appropriate acceptable way to conduct animal studies?

A. Absolutely. The question he is asking is what would you routinely see in a person who is this recreational user and only uses one tablet every time they go to a rave once every month. That's the kind of question he is trying to address.

Q. Let's make sure we are talking about the same paper. There is a 2007 study of Baumann, Wang and Rothman?

A. Right.

Q. MDMA neurotoxicity in rats: a reappraisal of past and present findings, Baumann et al. 2007. That's the paper we have been discussing?
A. It is.
Q. I take from the answer you just gave that you think that is a useful tool in measuring neurotoxicity in animals then translating those findings to an average recreational human user?
A. Yes.
Q. To the extent you would be interested in increasing dosage, you would be measuring the potential harms to heavy users?
A. Heavy users or people who are very sensitive to the drug. That's always going to be part of this discussion. We are talking about average responses and there are always going to be those folks on either side of the bell curve who are extraordinarily sensitive to the drug. So whether they don't metabolize the drug very well or their brain serotonin systems are exquisitely sensitive to a drug like this, you are always going to have those folks in there as well.
Q. That sensitivity is different from confounds such as mental health?
A. No, it could be the same thing. It could be that they have got a serotonin system that's not functioning normally anyway and that's expressing and they have a tendency towards depression. Maybe they are not really depressed so long as

everything stays in a normal routine, healthy way, and now they put a drug on top of it that further compromises that system and it pushes it down. That sensitivity sets them up both for problems with the drug as well as problems with the mental health issue.

Q. There are a variety of sensitivities that can affect the way a person is going to respond to MDMA?

A. Exactly.

Q. Some of those are mental health related, some of those are iconoclastic individuals brain chemistries different from mental health diagnoses?

A. Right or could be associated in one way or another.

Q. I would like to move to your own summary report. Did you yourself draft that report?

A. I did.

Q. I take it no changes; you stand by its contents?

A. Yes.

Q. In that summary you talked about MDMA's association with serious toxicities of the liver. In its acute phase, when someone takes MDMA, you would expect to see a change in liver enzymes, is that correct?

A. Yes, I would.

Q. That's because the function of the liver is to process -- that's what it does.

A. This family or group of drugs are somewhat notorious for

changing the hepatic enzymes that are responsible for metabolism.

Q. Distinguish acute versus chronic effects; when you speak of serious toxicities of the liver, you just described the fact there are significant acute effects to the liver during a period of use?

A. Right.

Q. But those pass through, the liver regenerates, correct?

A. Recovers, yes.

Q. Recovers from that acute phase?

A. Correct.

Q. When you say serious toxicities, are you speaking of the acute phase?

A. Yes.

Q. You talked about cardiovascular harm as well?

A. Right.

Q. When Mr. Chung was inquiring you spoke of a number of cardiovascular harms, elevated heart rate, increased blood pressure, a number of other things?

A. Right.

Q. We are again speaking of the acute phase with respect to those cardiovascular effects?

A. Yes, typically unless you have a heart attack; then you are going to have chronic but yes.

Q. You also say in your summary MDMA causes hyperthermia much

like amphetamines. Just to clarify, hyperthermia generally means elevated body temperature?
A. Yes.
Q. MDMA causes hyperthermia in its acute period just after ingestion?
A. Right. As I explained, it interferes with thermal regulation and so the environment plus that is what causes the hyperthermia.
Q. That has not been shown to have that chronic effect?
A. No. Once the drug is gone, that effect is gone.
Q. Your next point in the summary was that heavy MDMA use has been associated with neurocognitive impairment. We have already discussed that. That refers to the neurotoxicity issue that you and I have just been discussing and that you discussed with Mr. Chung?
A. Correct.
Q. I don't know whether you can put a number on this but when you say heavy MDMA use in your summary, say what you meant by that in terms of both dosage and frequency, separating them, if you will.
A. I think that's a critical point. With MDMA use compared to the animal models, we rarely do repetitive exposure with animal models, again for logistic, practical reasons. But there may well be an accumulative phenomenon that's going on with MDMA. That has not been looked at. This is a big question we need to

address with future research. So if you have somebody that's exposed let's say in a 24-hour period to 2 or 3 tablets of Ecstasy, they are getting about 300 milligrams per kilogram of the Ecstasy in the 24-hour period.

Q. You said 300 milligrams, 2 to 3 tablets. I know you were present when Mr. Parrott testified; he characterized the average tablet dose at 70?

A. 70 in England.

Q. Is there a different figure that's been demonstrated in the United States?

A. Yes. It varies. There are some places have been up as high as 120 milligrams, so it does vary on batches. I was also talking to Dr. Parrott. He said now they found some batches that don't have any Ecstasy in it but they are being sold as Ecstasy. That's one of the problems with this world. You don't always know how much of the drug you are going to get or if your going to get another drug in combination with the Ecstasy, so that confounds our interpretation of the human data when we see something or we don't see something, is it because the drug was there or it wasn't there or there was another drug there. So that's always an issue.

Q. I interrupted you to clarify. Continue.

A. The point I am trying to make is that if this person does the same routine every week for a year, even though they are not looking at the 5 to 10 milligrams per kilogram that we look

at in our intense exposure but the accumulative exposure to the drug is much higher over the course of a year, what does that mean. In all honesty we don't know what that means because our animal research has not looked at this in specific, but almost all of our human research has that confound and it doesn't know what to do with it.

Q. The frequency you just described would be associated with heavy use and it's distinct from the moderate, average recreational user, correct?

A. I would say that the average user probably wouldn't be using it on a weekly basis. They certainly could be using those doses on a monthly basis or every other month kind of basis. Someone doing it weekly you would put into a category of more intense use.

Q. Staying with this moderate user versus heavy user distinction, are you aware of data in the United States that attempts to categorize the percentages of users who would qualify as heavy users within the definition you just described?

A. I have looked for that and if you know a source let me know. I have not been able to find that although Great Britain and Australia who have big Ecstasy problems, they have looked at that. For example, in Great Britain there is anywhere from 1 to 3 percent of the people in their treatment. So this is treatment for every drug abuse issue, alcohol, cocaine, what

have you. About 1 to 3 percent are being treated for Ecstasy problems. So that would suggest kind of a number, you would have to do the math in terms of how many are using what have you.

Other studies have suggested that, like the Bruno study, there is this 20 percent, those users who are exhibiting dependence, significant dependence, and does that mean they are all addicted or just physically dependent, trying to avoid withdrawal. It doesn't equivocate that very well. It does say there is a significant proportion of these people who go on to become moderate to heavy users.

Q. Back to where you started with that point, if the percentage of people who report, who sought treatment for MDMA-related issues would be an indicator of the percentage of users who are categorized as heavy users within the criteria we have just described?

A. Correct, if you can do the math. What I said is 1 to 3 percent of everybody that's in treatment is there because of MDMA, so you have to figure out what's the number of Ecstasy users and then calculate how many are actually in treatment, then do the math.

Q. The answer wouldn't be 1 to 3 percent; it would be something different based on the total number of MDMA users?

A. Exactly. One of the things Kish mentions in his papers, he says about 40 percent of those people, those subjects that were

in their study described the process of tolerance and dose escalation. So we know that Ecstasy does cause tolerance. That's a fairly common phenomenon. People start to escalate.

Here again, we don't have a lot of research as to what that means. Once tolerance occurs, does that mean the body or the brain has changed in some basic neurobiological ways, is that a good thing, a bad thing, and they start to escalate their doses. Are they sensitized. Sensitization is a phenomenon with psychostimulants.

We see it with cocaine and methamphetamine which means that you start off with lower doses but as you use it over a period of time, you find that the system becomes more and more sensitive to the drug and not less and less sensitive, so we don't know what sensitization looks like with Ecstasy. No one has really looked at that very carefully.

Q. We will talk more about that in relation to dependence. I am moving through your summary. We will get back to your points. The next point you make in your summary relates to fatalities. Let's talk about that. You say deaths from MDMA abuse are comparable to those linked to methamphetamine and cocaine abuse. What do you mean by comparable; do you mean the fatality rate, that MDMA causes as many deaths as cocaine?

A. This again comes from some of the Great Britain studies and Australia studies. These investigators have concluded, one of the studies looks at, it's a fairly complicated formula, they

look at availability, they look at seizures, look at things that measure how much of the drug is being used and they concluded that if had a fatality potential similar to cocaine and amphetamine.

Q. Can you name the study you are describing.

A. It's Schifano.

Q. There is a Schifano study; I want to make sure we are talking about the same one.

A. There is another called King study that I think I indicated that they also do this comparison between methamphetamine and then a third one is the Kaye study and they are looking at Australia and trying to equate, and they conclude that the toxicity, the lethal toxicity is fairly similar between all of them.

Q. Let's talk about that in context of the Schifano study. The Schifano study looked at, distinguished between related death, cocaine or MDMA related deaths, and causal deaths, did it not? It drew a distinction a death which is related to ingestion of the drug and caused by the drug?

A. Correct.

Q. That distinction was that a death was related to the drug if the drug was present in the system of the person who died when they died?

A. Correct.

Q. Or when examined shortly thereafter?

A. Right.
Q. By that logic a person who was under the influence of MDMA and stepped off the curb and was hit by a drunk driver would be called an MDMA-related death?
A. Correct.
Q. Not caused by MDMA but related to MDMA?
A. Yes, that's fine.
Q. They drew a distinction and looked more carefully at those cases where coroners have listed the drug as the cause of death and teased out those numbers in term of fatalities?
A. Yes.
Q. With respect to MDMA, do you recall figures in Schifano?
A. I don't recall breaking them down to that degree but it seems like they start off with 800 versus 600 then they start to break them down into their packages.
Q. With MDMA it would help you to recall that there were 104 MDMA-caused deaths in 10 years, approximately 10 per year?
A. That would be fine.
Q. Is it your recollection that cocaine-caused deaths were similar?
A. No, they would have been higher than that.
Q. When we compare fatalities, in causation, not relationship but causation, MDMA is less likely to cause fatalities than cocaine?
A. Yes. What does the drug itself do and you would also keep

in mind that the doses these people are exposing themselves are going to be much different. The cocaine person is going to be on a cocaine binge sometimes so you are going to have a much higher dose.

Q. That wasn't known in the study?

A. No.

Q. That variable was not accounted for in that study?

A. It was not.

Q. So the conclusion of that study is that cocaine causes more fatalities than MDMA?

A. Correct.

Q. You mentioned two other studies; they used different variables?

A. They did.

Q. The bottom line of those studies is the same, that is, that cocaine causes more fatalities than MDMA?

A. Correct. They are comparing with amphetamines as well. As I recall, the King study makes a statement they are kind of equivalent in terms of their mortality potential.

Q. Let's go back to an area we were discussing before, that's dependence. We have touched on that in a number of ways; we have all touched on it.

A. Right.

Q. Would you agree with the statement MDMA is not addictive but has addictive potential?

A. Well, those almost sound like they are mutually exclusive. I would say that under normal recreational uses, the likelihood of addiction is fairly low but it does have addiction potential with escalating doses and all those qualifiers.

Q. Those would be for the hard to quantify but recognized heavy user population we discussed?

A. Yes. Almost by definition, if you are addicted you are going to be a heavy user because you have compulsive behavior and you need to use the drug.

Q. I take it from that, a person who used with level frequency over time once to twice a month but continued to use at that rate would not qualify as addicted?

A. They wouldn't satisfy that compulsive behavior definition of addiction, that's correct.

Q. You are making reference I think to the DSM criteria for dependence?

A. World Health Organization definition of addiction, right.

Q. One of those factors is compulsive?

A. Correct. The distinguishing feature there is that the behavior is so overwhelming that you want the drug, you need the drug despite the fact that it's having some fairly negative consequences in your life.

Q. When we talk about heavy use that invokes this addiction potential in MDMA, again, we are very limited in our data as to what percentage of users we are talking about?

A. Correct.
Q. That takes us back to the same question we talked about earlier, number of people who report for treatment, number of people who are admitted to emergency rooms, that kind of data would be useful in trying to understand.
A. It would, although the emergency room data, so many other things are going on there, a lot of times people who show up in emergency rooms are people who may have their first exposure to this drug and they don't know what they were doing and took too much, whatever.
Q. Dr. Parrott said that unlike cocaine users even heavy users generally decline in their use of MDMA; would you agree with that?
A. I have certainly heard that that's the case for a lot of those users.
Q. Although there is escalating use for some period, we generally see a decline?
A. Right.
Q. That's not true for cocaine?
A. That's correct.
Q. Or heroin?
A. That's correct.
Q. It's a different kind of addiction. Cocaine users will use and use until the money is gone and the life has run out?
A. That's correct. It's sort of a 2-phase, and that reflects

the psychedelic, hallucinogenic serotonin piece, and the addicting, euphoric, energizing dopamine piece and this interaction between those two systems.

Q. You talked about the differences between the drugs and the stimulant and hallucinogen properties. I am going to come back to the 2001 sentencing commission report characterized as one of the concerns, one of the harms of MDMA is its both stimulant and hallucinogenic properties. Do you recall that?

A. Yes, I do.

Q. We were talking about apples and oranges and that comparison between cocaine and MDMA. The same question that was asked of Dr. Parrott, that just because something has two properties instead of one, that is, both a stimulant and a hallucinogen, that doesn't make it doubly dangerous, does it?

A. In principle I would say that's true, but in regard to this drug, that's the basis for its appeal to the young population. They love the hallucinogenic, psychedelic enhancing of sensory elements. That's why they go to the rave. The rave is filled with all sorts of sensory things going on. They love the stimulus piece. It gives them the energy, it sort of reinforces.

You can kind of imagine that combination would be very fascinating to a young person. It's a hug drug. It's got this entactogenic property that they really like. It enhances love, at least as they define love. But on top of that you are

stimulating that mesolimbic dopamine pathway so you are getting the reward. This interaction is very appealing. That's why it's particularly dangerous, particularly problematic for that group of people.

Q. You just made an interesting leap. All the reasons you just described are reasons it's more attractive to a user, correct?

A. Particularly youth.

Q. You described what you define to be more attractive but you leapt to more dangerous. I take that leap to simply be if it's attractive to youth, it is by definition more dangerous?

A. We know that the youth population is particularly vulnerable to effects of drugs. We know they are more vulnerable to alcohol, they are more vulnerable to smoking. I can't think of a drug, there is probably some exception to that rule, the reason is that in adolescents and even in adults, young adult stage, brain systems are still developing, serotonin systems, dopamine sometimes.

All of these things are still coming together and if you start to sprinkle neurochemistry on top of that, the data suggest, even marijuana, use of marijuana during adolescence or during the developing brain will change the way that brain develops and what it looks like when they become an adult.

Q. What you have just said is essentially true for all dangerous drugs?

A. It is. So if you have a drug that is particularly appealing to that population, then in a way you are sort of lighting a match to the fire. You are bringing those two things together and increasing the likelihood that you can cause problems for this person as their brain develops.
Q. The region you just entered into is far more cultural and sociological than psychopharmacological, correct, that is, psychopharmacologically speaking, the combination of stimulant plus hallucinogen properties is not a double in effect?
A. Well it's a more intriguing effect to these kids; as you know, adolescents are all into intrigue and new experiences. So it gives them this unique combination of pharmacology that is very appealing to them.
Q. You just made a leap into behavior and culture again rather than rooting your answer in psychopharmacology.
A. I am not sure you can separate these things quite honestly. Maybe that's the neurobiology in me. I sort of see the world through a neurobiological window. It's hard for me to make the distinction because I think that they connect with each other.
Q. We have touched on this before and you mentioned the significance of emergency room data. You are aware that the commission looked at and mentioned emergency room admission in its consideration of harm, correct?
A. Right.
Q. And you would agree that emergency room admissions are an

appropriate indicator of harm?
A. Correct.
Q. You are aware of the national survey of drug use and health?
A. Yes.
Q. And that is an ongoing study and they have had a number of reports that track usage of particular drugs?
A. Right.
Q. Are you aware of the Dawn data?
A. I am.
Q. With respect to emergency room admission?
A. Yes.
Q. According to this data approximately 6 million people use cocaine resulting in approximately 550,000 emergency room admissions?
A. Right.
Q. Equating to about 9.3 percent of users admitted to emergency rooms?
A. Yes.
Q. With MDMA approximately 2 million users with 15,000 admitted to the emergency room?
A. Right.
Q. That's equating to .7 percent admission rate among users?
A. Right.
Q. So by that metric certainly we would say that MDMA is less

harmful than cocaine?
A. Yes, numerically there is certainly that difference. If you look at the data, you will also see that those that end up in emergency rooms because of Ecstasy use tend to be significantly younger than those who end up in emergency rooms because of cocaine and they also tend to be healthier which goes to the issue of there is this unique young population that's particularly attracted to this drug and they get into trouble with it sometimes.
Q. A significantly smaller percentage of them than cocaine users?
A. If you are just going by numbers, yes.
Q. The methamphetamine portion of users admitted to emergency rooms is also significantly higher than MDMA?
A. I would expect it to be.
Q. I don't believe you were asked about systematic reviews and their role in the research. Are you familiar with that term?
A. Like meta-analysis?
Q. Exactly.
A. Yes.
Q. Properly controlled are meta-analyses a useful tool?
A. Absolutely. I think they give you a lay of the land.
Q. Is the Rodgers 2007 study a good example of a well-done systematic review?
A. I am not aware, I know the study but I did not examine the

details in it. So I would leave that to others, Dr. Parrott and others.
Q. In contrast to a systematic review there is another kind of study called a narrative review?
A. Yes.
Q. Am I correct that narrative reviews, the value of narrative reviews is dependent on the selection criteria used by the reviewer?
A. Absolutely.
Q. Also by the extent to which the reviewer includes data which contradicts or calls into question their conclusions?
A. Correct.
Q. So a well-done narrative review would list not only those studies which ultimately support the conclusion of the reviewer but also any studies which reach opposite conclusions and then would compare the two?
A. Right.
Q. We talked about confounding factors. You made an important point with Mr. Chung that polydrug use is a confounding factor?
A. Correct.
Q. Most Ecstasy users are polydrug users?
A. Correct.
Q. You are interested in studying the co-effects of MDMA with other drugs?
A. Yes.

Q. You think that is an important question for research?
A. Yes.
Q. However, we talked earlier about ways in which the commission and this court are as nonscientists, as lawyers and judges attempting to assess harms for purposes of criminal penalties, attempting to separate out the isolated harms of MDMA. Would you agree these are two different tasks?
A. They certainly are related tasks. From a scientific perspective it's difficult to understand interaction if you don't understand what drugs do by themselves. So the isolated approach is always helpful in terms of interpreting the more practical interacting issues although sometimes it can lead you down a road that you don't want to go and tell you something that is not very useful.
Q. What I take from all or our discussion about all of the years of MDMA study is that because of the prevalence of polydrug use and the ethical and legal and other limitations on isolated MDMA studies, the field is fairly new in terms of psychopharmacologists absolutely isolating the effects of MDMA alone, correct?
A. In humans?
Q. In humans, yes.
A. And the reason is, boy, it's really hard to find these people.
Q. To the extent that studies are able to isolate monodrug,

MDMA-only users and compare them with nondrug users, those are pretty useful in helping us answer the question about the isolated impact of MDMA. Am I correct?

A. But there are some landmines there and that is that in finding a population that only uses Ecstasy, have you also found a population that has other factors that you may not be aware of that in and of themselves cause the behavior of only using Ecstasy but does not generalize to the big population that are polydrug users. See what I am saying?

Q. I do, but that would be in terms of psychopharmacological analysis, what is the effect on the brain of this drug?

A. Let me give you an example. This population does not use any other drugs. That tells you something about this youth, this group of adolescents, young adults. It tells you something about their environment is going to be different than these other people.

It tells you probably something about their attitude towards risk, what does risk mean. We know that risk, high risk behavior is very predictive of tendency towards addiction. It may tell you something about what's the likelihood that this group would ever get addicted to this drug. It's probably very small because they don't have that tendency. And it tells you something about what's happening in the community, would the community tolerate heavy use of this drug.

There are all these factors that have gone into

isolating a very small group. If you come and you do a study on that very small group and these other factors may be critical issues for determining the outcome you want to measure, you don't see much outcome in these folks because they don't have those factors.

Q. Understood. Another way of saying that is in the rest of the world, in the analysis of polydrug users with many of the confounds that have complicated the research, you are better able to test things like addiction potential in polydrug users which is the more common effect?

A. And you are probably better able to detect or to measure things such as toxicities, acute and long-term toxicities, because some of the toxicities that MDMA or a drug might cause have to do with how they interact with these other drugs or how they interact with a body that's been affected by these other drugs, and that's not going to be present.

It also may have to do with one of the ways they design or find their subjects. They say they used one tablet, or one MDMA tablet. Well, maybe these kids, because they are kind of aversive to risk and they are concerned about what might Ecstasy do to me. They go in very conservatively and cautiously and they kind of nibble on the tablet or they don't eat the whole tablet or they heard that heat can worsen the likelihood of causing side effects with this so they are making sure they are drinking lots of water so it won't cause a

problem for them. Or we had discovered a while back that Prozac protected against the damage caused by Ecstasy, so maybe they took a Prozac from mom and dad's medicine cabinet.

I am just giving those as examples of their approach to using Ecstasy might be very different than someone who is very high-risk oriented and has lots of drugs and their attitudes and strategies can be distinct.

Q. All the factors you just described about what might be confounding elements in an MDMA-only user survey, that's not based on your analysis of any particular study; that's a hypothesis about what might occur in such a hypothetical population?

A. That's correct, but it also gives me pause when I try to interpret and extrapolate what I found in this population to more global presentation.

Q. If your goal was to understand the pure and isolated effects of MDMA, you would rather have a study with MDMA users only than on polydrug users, correct?

A. So long as I put that caveat in there recognizing this may be a very unique population so whatever happens, you've got to be careful in terms of interpreting its significance.

MR. RORTY: Thank you very much.

No further questions.

THE COURT: Mr. Chung.

MR. CHUNG: No redirect.

THE COURT: From your perspective, Dr. Hanson, as a researcher, what is the best way empirically to try to measure the harms from a particular drug?

THE WITNESS: I guess it depends on what harms you are interested in. It's always hard to do the global analysis and say let's just talk about harms and adverse effects. You also almost have to focus in because if it's very global you miss stuff. But if you can focus in and say let's talk about the cardiovascular harms, how would this affect that, or how does this affect your liver function. Those are relatively easy to measure. We can hook you up to machines or take your blood and analyze it and get a pretty good sense as to what's going on.

It becomes more difficult when you get into behavioral analysis because that's so complex. A person could do one thing under one setting and it looks perfectly normal but they do the same thing in another setting and it looks pathologic or it's problematic. How do you make that distinction. Did the drug cause that. It looks like a normal behavior but the problem isn't so much behavior but it's their interpretation of the environment and deciding what's the appropriate behavior to put into that setting.

So those things are very hard to analyze. And then we have the longitudinal issues. I mentioned with methamphetamine we have just now found out that meth-dependent people have a five-fold increase in the likelihood of developing Parkinson's.

This is something they started 20 years ago. How do I link what they did 20 years ago with what's going to happen to them down the road.

Those are some of the problems we wrestle with with drugs luck Ecstasy that we know is really having a profound effect on brain chemistry. We know that. Now it's having a profound effect in the immediate future and there is a discussion as how far does that go and what does that cascade of events do. At the end of days you come to a person just before they are buried and you say, how was life, and they tell you, it was great, I enjoyed it, then you would say, OK, I guess you didn't have any big problems with drugs

On the other hand if they say life was horrible, I had all kinds of problems with my family, I couldn't keep a job, then you would said, oh, it likes like maybe drugs caused a big problem for you. So hard to do, don't know that's very satisfying answer, but it gives you a sense of how difficult the question is.

THE COURT: In your testimony today you have talked about the particular attractiveness to young people of MDMA because of the combination of both the stimulant and the hallucinogen.

THE WITNESS: Right.

THE COURT: At the time of the Sentencing Commission report to Congress, there was a wave of MDMA cases around the

country. Over the last 10 years, what have you seen from your vantage point in terms of the use of MDMA?

THE WITNESS: This is a drug that's very sensitive to perceived risk and when that youthful population sees the drug having potential of severe toxicity and problems, they tend to move away from it. So it's interesting. You can argue whether the data were completely accurate or whether we did the best thing, but it's interesting that after that 2001 where we really had a major epidemic, 9 percent of our youth were trying and experimenting with this drug, it dropped. You get to 2005, and it drops down to about 3 percent. That's big cut over a period of 3 to 4 years. Now we are starting to see a resurgence, not a dramatic resurgence, but we are back up to about 4-1/2 percent, so we have come up from the bottom.

THE COURT: Do what do you attribute that?

THE WITNESS: Lloyd Johnston is the one who does monitoring the future. This is a NIDA-sponsored survey. He says that there is a good correlation between perceived risk of the drug and the likelihood they would use it. So as they analyzed their surveyed risk, they saw risk, perceived risk for Ecstasy went up and use went down. Now they are seeing perceived risk as going down and use is starting to come back up. So, there is that connection and there are lots of factors that contribute to perceived risk.

One of the factors is that the media is really

covering this FDA-approved clinical trial of Ecstasy for PTSD. I am not saying it's good and I am not saying it's bad. Personally I have no problem and I wouldn't be surprised if indeed it is of some value in treating PTSD. We use methamphetamine to treat ADHD. We use some of these drugs of abuse to treat. They have perfectly legitimate medical use.

It's when we are throwing it out and people are using it on their own and they are being their own doctors or using it recreationally, we have no control over that, you get into trouble with it. Having said that, as you took to youth, I teach a class at the University of Utah called common medicines. We just talk about drugs. We talk about Ecstasy and I get some feedback. I say what do you think about Ecstasy, what's your attitude. They say it's not a very harmful drug. And I say why do you say that. They say we just read in the newspapers it's being used to treat PTSD. How could it be helping these people who are struggling with PTSD and be harmful.

That kind of attitude. I am not saying those kids will go out and use it. It's certainly the perceived risk issue that's happening. Again I am not saying that's bad or that's good, I am saying that is a reality. It's attractive, they go out and use it. The more they use it, the more people you are going to have that will get into trouble with it. That's just basic pharmacology.

THE COURT: You say you have seen an uptick.
THE WITNESS: Correct.
THE COURT: Can you put a timeframe on that for me.
THE WITNESS: It hit bottom 2005, it kind of stayed around there for 2005, 2006, and 2007 it started to climb, then our latest data, we have not got the 2010 data yet, the 2009, it's come up to about 4.5, 4.6 in high school seniors.
THE COURT: I reviewed with others the principal bases on which the Sentencing Commission rested its report to Congress. I would like to hear your comments on those three observations from the report. I am reading from page 5 in which the commission stated that it shows a greater penalty structure for MDMA trafficking than for powder cocaine trafficking because, 1, unlike MDMA, powder cocaine is not neurotoxic. I will take these seriatim, if you would comment on that.
THE WITNESS: Probably some of that came from my testimony because we find that in the animal model and in humans, we have gone back mostly have done postmortem studies to try to analyze if it's disruptive to things such as serotonin systems or dopamine systems, whatever, and we don't see a lot of persistent neurotoxicity. It doesn't have that pattern like the amphetamines and Ecstasy for serotonin. We don't see the deficits.
In my laboratory we tried, we thought way back when

that cocaine would probably look a lot like the amphetamines and we didn't ever see persistence in toxicity to either the dopamine or the serotonin system like we do with Ecstasy and like what we do with methamphetamine. That's probably where that statement came from. Based on that that's true. We don't see that kind of persistent toxicity that you see with the amphetamines.

(Continued on next page)

THE COURT: The commission went on to note as a second reason that powdered cocaine is not aggressively marketed to youth in the same manner as MDMA.

THE WITNESS: That is true. It doesn't have the appeal to the young people that MDMA does. And a lot of it is this perceived risk issue, that they don't see MDMA as a risk for them and so they are more inclined to do that.

Even kids in Salt Lake City are not going to use cocaine, but they will MDMA. We know that that can be terribly dangerous, so they are willing to go out and try it. So, yes, we see it and, as a general rule, the population that is most affected is going to be a younger population.

THE COURT: We heard testimony that there comes a time generally in the use cycle of MDMA that people simply quit --

THE WITNESS: Right.

THE COURT: -- MDMA. Can you explain that to me because it seems so different from other drugs like cocaine?

THE WITNESS: Some of this is just conjecture on my part because it would be very interesting to go and get these individuals who had used compulsively and then they just stopped. If you could have a brain image of what their brain image looked like before and what it looked like afterwards, I wouldn't be surprised if there isn't maybe a pathological explanation, that is, they could have used the drug in an intense fashion for so long that it compromised systems, maybe

systems that have to do with motivation, maybe systems that have to do with interpretation, whatever. But now because that's been compromised, they are no longer interested in the drug per se. So it may not reflect a good thing. I mean, it may reflect a good thing, I don't know. It may actually reflect a pathology but just reflect that they finally figured it out, they grew up and they moved on.

THE COURT: The third factor that the commission cites is that powdered cocaine is only a stimulant, but MDMA acts as both a stimulant and a hallucinogen.

Now, you did discuss that on cross-examination. Putting aside the attractiveness of that combination to youth, as you described, is there any scientific basis, any psychopharmacological basis that would suggest that that makes MDMA more dangerous or more harmful because it is both a stimulant and a hallucinogen?

THE WITNESS: I wouldn't say it is more harmful on a neurobiological basis because that gets into a different discussion of how the serotonin and dopamine interact with each other. Serotonin is a modulator of dopamine function, but it does -- and I think this was the intent of the commission -- it does help explain why this drug is particularly attractive to this very youthful population. The entactogenic feature of the drug is very exciting to them. They talk about, oh, when I take this drug, I just feel like I want to hug and love

everybody and it is fun to be around my friends and it is fun to be in that rave scene. This is very attractive to them. You don't get that with cocaine. So you lack that piece of pharmacology, meaning that cocaine would appeal to an older population whereas this appeals to the younger population.

THE COURT: You also discussed the fact that dosage amounts are different in the United States than what is typically seen in the Great Britain. Did I understand that correctly?

THE WITNESS: Yes. Partially, dosage amounts are different from batches, depending on where they come from, regardless of where they end up. You could argue that there are certain organizations that control the production end or trafficking of the drug and they may make some executive decision that, we want to optimize our profits on this product, so we are going to cut back on Ecstasy. Instead of giving them 120 milligrams, we are going to give them 70 milligrams, whatever goes into those kinds of decisions.

But if you are getting batches from different sources, then it may mean that the potency of the Ecstasy is different. And as I mentioned before, in some cases, it may mean that you don't have any Ecstasy, even though it is being sold for Ecstasy or it has got something else, it has been contaminated with something like MDMA. Now, MDMA, they are starting to get into dopamine toxicity with MDMA and it starts to look more

like methamphetamine and it does. So depending on where it is coming from there is no Good Housekeeping seal of approval when you buy this stuff. It is illegal, and there is no guarantee as to what it is that you are going to get even within the country you may find different batches with different potencies.

THE COURT: In your view, how significant is it in measuring the harm of a drug whether or not the drug has addictive properties?

THE WITNESS: Well, it is significant in terms of -- if it is addictive, then that means your use is going to be more compulsive and it is going to be less side effect and less negative consequence driven, and you are more likely to use higher dosages, and you are going to do those more frequently. And then you are just getting into the dose-dependent discussion, that is, the more you use, the greater likelihood you are going to pass the threshold for toxicity, and you are going to have problems with it.

And the process that leads up to addiction itself generally means you have used the drug quite a bit to get here. Your brain has basically changed. Addiction, we know now is a learned process that is embellished by pharmacology. So you kind of learn to use a drug and make it a part of your life.

THE COURT: Would you explain that a little further for me?

THE WITNESS: Addiction is a process of learning. We know now that a lot of the basic neurobiology to addiction is the underpinnings of what learning looks like in terms of what brain systems are involved. Alan Leshner, who is my predecessor at NIDA -- he was the director before I was the acting director -- he used to say that with addiction, what you have done is, you have hijacked the brain. So you have taken advantage of basic neurobiology but you have tailored it in a way that is now harmful to you.

So in that regard, you turn what used to be a casual behavior into one that has become a compulsive behavior and now you are going to use more and more of the drug and now you are going to get into the toxic levels of the drug and you are more likely to get things such as we have been discussing with high dose use of Ecstasy.

THE COURT: You were present and participated back in 2000 and early 2001 when the Sentencing Commission was looking at this. Now you are here today. Can you summarize for me what it is that has changed since May of 2001 when the commission sent its report? You have described in part that some of the technology has improved.

THE WITNESS: Correct.

THE COURT: What, from a psychopharmacological perspective, have we learned about MDMA since May of 2001?

THE WITNESS: I think we have learned that it is

probably quite a bit more complicated than we thought it was at that time, that there are a lot of complexities here. And while our research gives us some answers, there always seem to be confounds there that create some problems in trying to interpret the answers.

There is no golden bullet answer to this. There is no one-size-fits-all answer to this. It is very dose dependent. It is very environment dependent. It is probably dependent on the things that people bring to the experience.

This is what we call systems biology, and this is sort of a movement of where biology in general is going, but pharmacology is as well. And that is, we have to stop thinking about an isolated exposure of a single system to a single dose of drug and somehow generalize and extrapolate that to reality in life because that is not what life looks like. And that is the case with Ecstasy. There is not one answer that satisfies everything. There is probably a lot of answers that are out there. And in our future, we have to figure out how to integrate it. And for folks such as yourself, you have to figure out how to use this complexity in order to make your decisions.

THE COURT: I am always groping down a dimly lit corridor.

THE WITNESS: That is why my perspective is fun, because I get to give you the information and then give you the

charge to go ahead and be wise with it.

THE COURT: Are you aware of any studies that have directly found neurotoxicity in humans?

THE WITNESS: Well, using the definition that I gave, that is, that you have interfered with normal functioning -- and there have been a number of them and there have been reports. Some of it is subtle. Some of it is more profound. Some of it is anatomical. Some of it relates to the markers -- crude as they are -- of serotonin systems.

But in every case there have been other studies using different populations and usually there are some subtle distinctions in terms of how they pick their subjects, how they dealt with those subjects. But in almost every case, someone has come and said, well, in my study we didn't see that same thing. So we are missing something, and I don't think that it is because -- it is not a good guy, bad guy thing. There are good scientists and there are bad scientists. I think that they have just constructed their studies in different ways, and we are not clever at this point enough to know what are all the critical factors and we are not controlling for them and so we are getting these different measures. And that's why the meta-analyses are useful because they allow us to go back and say, while we may not get specific answers, it does tell us that there are a lot of things going on here and we haven't figured out quite how to drill down and come up with the

overall answer to what is going on.
THE COURT: Thank you, Dr. Hanson.
Do counsel wish to make any further inquiries of Dr. Hanson?
MR. RORTY: No.
THE COURT: Anything further, Mr. Chung?
MR. CHUNG: None, your Honor.
THE COURT: Dr. Hanson, you are excused as a witness. You may step down.
(Witness excused)
THE COURT: Does the government have any other evidence to offer?
MR. CHUNG: No, your Honor.
THE COURT: Does the government rest?
MR. CHUNG: Yes, your Honor.
THE COURT: Do the defendants have any further evidence to offer?
MR. RORTY: No.
THE COURT: Do the defendants rest?
MR. RORTY: Yes.
THE COURT: Two things. One, I made an inquiry last week of the Sentencing Commission staff because I was interested to learn whether they maintained any statistic on the number of MDMA cases sentenced in the United States by year. I could not find that information looking on their web

site and in their compendium of materials that they sent to me. But I was able to speak with a research director at the Sentencing Commission who provided me with a chart titled "Number of MDMA Cases, Fiscal Years 2000 to 2009." And the source is a data file at the commission.

Simply so that it is part of the record in this case, in the event that the parties want to refer to it, I have had copies made and my law clerk will distribute them now to counsel. If I had thought of this earlier, I would have distributed them earlier, but better late than never. And this may be dated, as you are already well aware of, but if not, you have got it now.

Generally, I would think that one could interpolate from sentencing the recognition that, one, cases take time to be made, indicted and sentenced. And so the tabular data, I think, would correlate well with Dr. Hanson's testimony, albeit, we have about a two-year delay because it revealed a peak in 2003 of 906 Ecstasy sentencings. Thereafter, there was a precipitous decline and it has rumbled around 450 in 2008 and 2009.

Now, I think I said yesterday that I would afford the parties an opportunity to submit a memorandum to me in connection with this matter after you have had a chance to go over the record. I will give you what time you need, but then I would also like to set this matter down for a sentencing.

Obviously, I have an issue to address here that I am likely going to write on.

How much time would the parties like to submit a post hearing memorandum?

MR. CHUNG: Your Honor, may the parties have just a moment to confer?

THE COURT: Absolutely.

(Discussion off the record among counsel)

MR. CHUNG: Your Honor, is the Court contemplating simultaneous briefing or sort of more staggered defense-government response.

THE COURT: What we could do is have simultaneous submission and then I would give each side a few days to make any short reply to what they saw in their adversary's submission. I think that may be the best way to proceed.

MR. CHUNG: OK. One moment.

(Discussion off the record among counsel)

MR. SPORN: Your Honor, while counsel is caucusing about that, let me tee up one other issue that may or may not affect our scheduling, and that is the custodial status of my client.

Absolutely none of us are presupposing any outcome here, but it occurs to us that if your Honor were to find that the guidelines as they are may not be appropriate and find that some other lower guideline would be appropriate, we may end up

in a guideline range, before we ever get to 3553 considerations, that approaches the time that Mr. McCarthy has already been in custody. He has been in custody now approximately 14 months.

THE COURT: I am well aware of that.

MR. SPORN: I know you are, your Honor, and I know that is why you want to proceed to sentencing as quickly as we can, and we want that to and nobody wants him to be in longer than the guideline range. And I have to say that Mr. Chung has not been unsympathetic to that possibility, and we have been talking about it.

It was never really contemplated that he was going to be in custody. There were a set of conditions set for his release. We have not been able to meet them. So Mr. Chung and I are now talking again about perhaps tweaking those conditions to perhaps permit his release and, if we can agree, we come with a package or, if not, I may come and make an application because I don't want his status in custody to be a cloud on this inquiry.

Obviously, there is a lot of material to digest. We are going to want to marshal all of the facts that we heard in support of our argument, and I am sure that they are going to do the same and this is a time-consuming process, and I don't want your Honor to be in a position of having the fact of his custodial status to be a cloud over your Honor's deliberation.

MR. CHUNG: Your Honor, what I can represent is that Mr. Sporn and I have had discussions regarding this very issue ever since Mr. McCarthy's arrest. And as Mr. Sporn just indicated, there is a bail package set, he just has not been able to meet it.

So what I can represent is that the government nor defense has committed to whether that bail package can change or whether an agreement can be made. All that I can represent is that I will continue to discuss on a short-term basis with Mr. Sporn that issue, and if we can come to an agreement, we will come to your Honor with a proposal. If there is an agreement, I am sure that Mr. Sporn will make that application, but we will do that in short order in light of the concern that Mr. Sporn just indicated.

MR. SPORN: I am just thinking about it while Mr. Chung was speaking, would it make sense to hold off of setting a sentencing date until we get to the bottom of that?

THE COURT: Obviously, if the defendant is able to meet a bail package by agreement with the parties, that takes a lot of pressure off of everyone. I don't sense the same urgency in sentencing his co-defendant who is out that I do in having anyone who is sitting in custody across the street or at the MDC.

I would like to hear what the parties have in mind with respect to a briefing schedule.

MR. RORTY: Here is the proposed schedule that assumes that Mr. McCarthy remains in custody.

Simultaneous filing on January 21st.

Simultaneous responses on January 28th.

Sentencing the second week in February. I believe it begins the 5th or 6th. I don't have a calendar with me. And perhaps if the Court does check, I think that the 21st is a Friday. The 28th is a Friday. And we are suggesting essentially somewhere two weeks from then to sentence.

But as the Court has said, if the Court is contemplating writing on that, the Court may well want to give itself more time following the completed briefing.

THE COURT: Why don't you see if you can talk further about this matter. I really think that my sense was that what you are proposing is an extended briefing schedule. If he is out, in the end, I don't have a problem with that, but I am going to want a little time and I am supposed to begin a three-month criminal trial.

I am going to suggest this.

Confer, and you can send me a letter in a couple of days and let me know what you propose and whether there is any agreement that can be reached. If not, I will fix a schedule taking into account what you are proposing or I will entertain whatever application the parties wish to bring before me and resolve the briefing then.

Obviously, I am not anxious to impose undue burdens on the lawyers. I think that you have all done a superb job in presenting this matter to the Court. And it has been a fascinating two days and fascinating days leading up to this, reading some of these materials and trying to come to grips with it.

I will not fix a sentencing date now. I will expect to get a proposal from you by the 10th of December with respect to a schedule for briefing here.

I think you should talk. I think you have been undoubtedly talking for a long time about this matter. It is hot on the skillet, so why not confer.

And then if we need to have some resolution of this next week, I can either hear an application, approve a proposal, hear an application. And if I grant the application, fix one briefing schedule. If I deny the application, I am going to fix a more rigorous schedule. All right.

MR. SPORN: Understood, your Honor.

THE COURT: I am sorry that I can't be more clear with you tonight.

MR. CHUNG: I think it has been a lot clearer than some of the issues that we have been discussing, but thank you.

THE COURT: Thank you all.

Have a good night.

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INDEX OF EXAMINATION

Appendix B

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF NEW YORK

UNITED STATES OF AMERICA,

PLAINTIFF,

vs. No. 13-CR-570(JBW)

CHIN CHONG,

DEFENDANT.

August 22, 2014

10:25 a.m.

TELEPHONIC DEPOSITION of DR. JOHN HALPERN, M.D., held at United States District Court - Eastern District of New York, 225 Cadman Plaza East, Brooklyn, New York, Pursuant to Notice, before CHARISSE KITT, CRI, CSR, RMR, FCRR, a Notary Public of the State of New York.

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BY: CHASE A. SCOLNICK, ESQ.

MR. SCOLNICK: Good morning, again, Dr. Halpern. This is Chase Scolnick, we're on the record here today.

THE WITNESS: Okay.

MR. SCOLNICK: Can we start by placing you under oath?

THE WITNESS: Yes.

DR. JOHN HALPERN, M.D., called as a witness, having been duly sworn, was examined and testified as follows:

THE WITNESS: John Halpern, H-a-l-p-e-r-n.

EXAMINATION BY MR. SCOLNICK:

Q Dr. Halpern, we have a lot of ground to cover today and I realize you're a busy man, so I want to get started by talking briefly about your qualifications.

A Sure.

Q Okay. I'm going to just lead you through that in a few questions, so we can kind of just get the substantive matters.

Is it true that you're a medical

doctor?

A Yes.

Q And you're licensed?

A Yes.

Q Did you go to or attend a residency program?

A Yes.

Q What was that in?

A In psychiatry.

Q And where was that?

A At the Harvard Longwood Psychiatry Residency training program.

Q And after completing your residency, were you awarded research fellowships at Harvard?

A Yes.

Q Go ahead.

A I had a Peter Livingston Award and was the fellow from Harvard Medical School for my research, as then I received government funding for my research and my training.

Q And since that training have you worked as a director or a psychiatrist in charge of coverage for hospitals in the Boston

area?

A I am director of coverage for the Division of Alcohol and Drug Abuse at McLean Hospital which comprises all elements of the clinical services we provide for substance abuse and those suffering with mental health issues as well. I also am the director of the laboratory for integrative psychiatry at my institution as well.

Q Are you also a professor at Harvard Medical School or associate professor?

A Yes. I have a professorship appointment at Harvard Medical School and that's specific to my research of the affects of hallucinations.

Q And in your experience with working in hospitals as an alcohol and abuse researcher and counselor, have you encountered people who have been addicted or abusing drugs before?

A All the time and pretty much on a daily basis in my work.

Q Is it fair to say you've been in contact and interviewed and treated thousands

of people who are suffering from drug related issues?

A It would be hard to put the exact order of magnitude, but since completion of residency in 1998, I'm sure it's well towards a few thousand people.

Q Are you also aware of national statistics and research involving substance abuse issues?

A I am.

Q And I understand you've been published a number of times in the field of substance abuse and psychologic substances. Is that right?

A That's correct.

Q And looking at your resume, it looks like probably around 60 different publications, between peer review articles, invited articles and book chapters, abstracts, and letters to the editor. Is that roughly accurate?

A That sounds approximately correct.

MR. SCOLNICK: Okay. I am going to offer your resume, your CV, excuse

me, as Defense Exhibit B to the hearing today, previously provided to the government.

(Defendant's Exhibit B1 so marked.)

Q Now, Dr. Halpern, I'd like to move on to the substance of your testimony today, and I want to just take a broad picture of what we're talking about before we get into specifics.

You're familiar with MDMA, the drug MDMA. Is that correct?

A Yes.

Q And you've testified about this before?

A Yes, I have.

Q Are you familiar with the Sentencing Commission's analysis of the drug MDMA conducted in 2001?

A Yes, I am.

Q And are you familiar with the current state of research regarding MDMA?

A There's a tremendous amount of research that is ongoing and published, but I

think I'm pretty well versed in the literature, yes.

Q Now, you testified before, I understand, that MDMA is a harmful drug. Is that still your opinion today?

A Absolutely.

Q Okay. Relative to other drugs, specifically cocaine, do you believe that MDMA is more or less harmful than cocaine?

A It is my clinical and expert opinion that MDMA obviously is less dangerous than cocaine. No physician could determine otherwise.

Q We'll get into that in some more detail. Regarding the state of research and understanding of MDMA, between 2001 and today, how has the understanding and research regarding MDMA's affects on the body changed?

A Well, broadly speaking, since 2001 there's been a better research system to track humans over time and to have a better understanding of the human/animal dosing rate to, you know, try to compare animal work to human work, primarily by myself, in making a

better attempt to control the heat compounds and construct our confidence in earlier studies, and there's definitely better technology since 2001. And that is the result of understanding how MDMA impacts, for example, the serotonin transporter in the brain.

Q What was the understanding in 2001, for example, involving serts?

A Well, it was believed that MDMA would be neurotoxic, would cause a decrease in -- the physical transfer binding would be decreased after ecstasy and it would stay that way. There's evidence that there's some sort of urine toxic event occurring from the substance. And since then we've known from research that with time that sert binding actually return to levels that are comparative to non-users.

Q So if I understand you correctly, this data, the scientific community or understanding in 2001 was that there were permanent changes regarding the sert or serotonin levels in the brain after use. Is

that correct?

A Yes. Particularly it's an important study by Dr. Kish, published in 2010, in which using newer or more advanced technology did not find serts in the transporters. And so there's no global massive production of brain serotonin transporter binding. And there's been no substantive study to invalidate Dr. Kish's work.

Q You mentioned that Dr. Kish's work found that there was no global mass production in serotonin levels or activity in the brain. What was the understanding regarding that in 2001? Was the belief in the scientific community that there was such a global reduction or --

A Yeah. There's -- my colleague McCann published in 1998, I believe, claiming that there was loss of serotonin transporters throughout the brain. And so that's -- that's been replaced, I think, with a much approved methodology and a more accurate -- a more accurate sert that was used by Dr. Kish that

wasn't available to Dr. McCann.

And so the 1998 data that I believe the Sentencing Commission relied on is no longer considered the current scientific conclusion drawn from the literature at this point.

Q You mentioned what the -- what the Sentencing Commission considered in 2001. Are you familiar with a document called the -- I believe the SSC or MDMA Report that the Sentencing Commission considered in 2001?

A Yes, I am.

Q And is it your understanding, based on these new findings and research techniques that you described, that the concerns and fears and research cited in the 2001 report has changed significantly?

A That's correct.

Q And based on those changes, it is your conclusion that the fears and concerns in the 2001 report have not been realized?

A That's correct. Not only has it not been realized in basic clinical research, but even looking at public health measures.

By now you would be seeing a much different picture from the public health standpoint were those fears to be realized upon those people having significantly abused MDMA.

Q And what type of public health measures are you referring to?

A Well, back then there were fears that MDMA use would lead to a whole generation that would be depressed or would not respond to antidepressants or would -- there would be a wave of Parkinson's disease, and none of those things have been realized. There was concern about addictive potential, and present we are -- it is obvious that MDMA is not reinforcing, causing crime addiction when, for example, cocaine is. And that, of course, is reflective quite obviously in other measures, such as the government's data on emergency room visits that, you know, close to 200,000 people a year showing up with cocaine as a permanent feature in the United States. We have less than, you know, anywhere from 8 to 12,000 a year for MDMA.

So it's just a dangerous thing for

America to present to our communities that cocaine is safer than MDMA.

Q Right. I think you mentioned some public health measures and some data from emergency rooms. I think it would be best if we can maybe look at the social metrics involving the two drugs or involving MDMA relative to other controlled substances, and then perhaps we can get more into the scientific research regarding brain activity, memory loss, those types of subjects.

So let's start with the relative societal harm caused by MDMA.

Are you aware of any studies that have compared the relative societal harms of a number of controlled substances?

A Yes. There's been a number of publications on this; most prominently was the work of Dr. David Nut, in England, who published about relative risk across drugs using a methodology assessment of harms. But there's other studies that rank harm of drugs such as, I believe a paper by Dr. Amsterdam, a colleague, that was published in 2010.

Another one by Dr. Morgan that was published also that year.

And I believe there was a recent study also published that surveyed physicians, asking their opinions, looking at a set of criteria of harmful drugs also.

Q Thank you.

Now, Doctor, you mentioned a number of studies that were conducted regarding the relative harms of controlled substances. Was there any consensus within those studies regarding their treatment or consideration of the dangers of MDMA?

A Yeah. They all ranked MDMA as much less dangerous than cocaine. There's no -- there's nothing offered in the data suggesting otherwise.

Q So that would be in each one of the studies you talked about?

A Yes.

Q All of the studies concluded that MDMA was, would it be fair to say, significantly less harmful than cocaine?

A Yes. Exactly what is reflected

whenever I speak with colleagues. I surveyed every physician in my division of alcohol and drug abuse, asking them just, you know, which is more dangerous, cocaine or MDMAs. To the last physician, exactly the same as what's in those papers, said MDMA is considered safer than cocaine, and it's obvious why.

We deal with cocaine, the damages from cocaine abuse on a daily basis. The number of times that we admit people for MDMA abuse is a prominent feature in their admission. This is an extremely rare event. I can't recall even the last time that I have admitted somebody because of MDMA use.

Q And in those studies, how did MDMA rank compared to, say, alcohol or nicotine, if you can recall?

A It ranked lower than all of those studies. Lower than cocaine and lower than tobacco.

Q And do you recall any statistics regarding comparative harms between MDMA and marijuana in those studies?

A It was ranked near marijuana. It

was ranked slightly higher than marijuana, I believe, by Dr. Morgan and as well as Dr. Amsterdam's paper, and I believe also in Dr. Nut's. But I need to look at Dr. Nut's study again to confirm them.

Q That's fine. I'm concerned about the timing here, the date of these studies. Have any of these studies, to your knowledge, been published since 2011, or since early 2011?

A Yeah, there are studies from other physicians. A few hundred physicians have published since 2011.

Q So is it your understanding that this data was not available at the time of the hearing in United States versus McCarthy, in Southern New York?

A Yes, that's correct. That's subsequent to the McCarthy Hearing.

Q You talked about your own experience, having dealt with thousands of people involved in drug abuse and treated them and also speaking with other doctors in your field. And is it your opinion that there is a

consensus regarding the comparative harms of MDMA regarding cocaine?

A Yes.

Q And what is that consensus?

A The consensus is that cocaine is more dangerous than MDMA.

Q Okay. I'd like to go on to some example as to why. First, is it your understanding or accepted understanding of the scientific community that cocaine is addictive?

A That is correct.

Q Is it your understanding, given the current state of research, that MDMA is addictive?

A No. It's not showing the reinforcing properties that are exhibited by cocaine. The vast majority of people who abuse MDMA do so in a time limited fashion and do not continue to ingest this in a repetitive pathological way that occurs in cocaine dependents.

Q I believe Dr. Parrot testified that MDMA is, quote, one of the least

addictive drugs, end quote. Would you agree with that conclusion?

A I absolutely enjoy whenever I can agree with Dr. Parrot saying something accurately, and that is one of them. Yes, I agree with that statement.

Q Well, we'll get into Dr. Parrot's research in a few minutes, but getting back to cocaine and MDMA. You mentioned that cocaine is addictive, whereas MDMA is not. Given your experience and research in the field, what are the societal harms related to an addictive drug?

A Well, it's -- obviously it's dependent on also the direct psychological affects of the drug or the intoxication as well as on the other end of it, just the health consequences that might --

So, for example, tobacco. Nicotine is highly, highly addictive and it is one of the leading killers in the world. So it's very dangerous. But in terms of it's impact on cognitive function and general sense itself, it's much less dangerous.

So it's more complicated than just those factors alone. Each drug has its own risk profile. But, you know, we look at things like, does it promote morbid illness and does it damage people's functioning in a clinical significant way. And if we just -- looking at it from that layman's perspective, what's the clinical upshot of, you know, being an abuser of a drug. You look at measures such as employment, their medical and mental health, and whether there's any observed deference in performance because of that abuse. And without a doubt, cocaine, you know, highly impacts people's lives, whereas we don't see that with MDMA.

Q Now, I want to get into that a little bit more. You said that cocaine would affect, certainly would affect people's health. Is that your testimony?

A Absolutely. It causes heart attack and stroke and overdose and it leads -- it's one of the leading drugs of abuse that land people in the emergency rooms.

Q And you've dealt with and treated,

I'm assuming, a number of people who have been addicted or having trouble with cocaine. Correct?

A Absolutely.

Q Is it your experience or is it the scientific consensus in the community that cocaine also has a negative effect on people's, we'll say, family relationships?

A Absolutely.

Q Could you explain that, please.

A Well, because this drug wears off really fast and has an acute craving, such that people will want to continue to use, and so they will spend a tremendous amount of money until they become dependent on it. And this pathological behavior will continue over days and longer. And then there's a period of where they, quote/unquote, crash and then they will wind up doing this again. And the amount of days that they wind up using expands. And the amount of drug they use expands.

All of the criteria says they are physiologically and psychologically dependent on the drug even though they know it's

destructive, even though they know it's hurting themselves.

People who use MDMA do not have such a pattern of abuse. They will typically take, you know, one or more pills on a single occasion and not on successive days, because acute tolerance builds. So somebody who takes MDMA, you know, the very next day, it will have a much more attenuated effect and there's no way to surmount that by taking more.

In fact, many, many, many people who consume this drug describe that it stops having the primary desired effects after several uses, and that then self limits how much people wind up going into this phase of life of using. Most people wind up moving on in their lives and stop using MDMA.

Q Thank you.

Have you noticed through your research or have you noted through literature a relationship between cocaine use, addiction, and crime?

A Well, again, absolutely. In one of the clinics that I'm -- that I work at, I

also have patients that are in the final stages of release from the Federal Bureau of Prisons, so they're in a halfway house shelter transitioning them, you know, to probation. And I have examined a number of people who were incarcerated because of their crimes with distribution for cocaine. And it's just remarkable how this very dangerous lifestyle will affect our communities. It's a real mess.

Q And when you say a very dangerous lifestyle, is that a dangerous lifestyle that's typically associated with cocaine use?

A The patients I'm thinking of are people who wind up being abusers of cocaine, who also are involved in the distribution of cocaine illegally. And invariably there's a tremendous history of associated violence, guns and gang collusion in these distribution systems.

Q And are those patterns also typical of MDMA users?

A No, it's not the same. There are, of course, distribution systems of criminal

enterprises that are distributing MDMA, but there's also a much different pattern of abuse and abuse by users themselves, so it's not the same. I'm sure there are criminal gangs who make MDMA sales a part of their enterprise, but there's many people who abuse this drug who seem to believe that within their culture that it's important for them to make additional MDMA available to friends and even family, and it's not about profit.

Q Okay. From your experience how is MDMA ingested?

A MDMA typically is ingested orally. However, there are people who will also nasally, you know, snort it, and also take it as an enema. I've had a couple of patients who were heavy drug users who also injected MDMA, but the vast majority of people ingest it orally.

Q Okay. And regarding cocaine, how is cocaine typically ingested?

A Cocaine is typically ingested through snorting powder cocaine or through the smoking of it, freebase, or a cheaper crack

variant.

Q And --

A Some people also will inject it, and some people will inject it as a speedball, so they inject it with heroin. And I myself at the government funded research in which I injected government sourced cocaine to show how cocaine causes local tissue, you know, suppression.

For example, the transmission of HIV from needles is more likely, of course, with cocaine, not MDMA. Another example of how dangerous cocaine is, apparently.

Q So there is a higher risk of HIV associated with cocaine use than for MDMA use?

A I would expect so. Because MDMA is not typically intravenously injected, whereas there is a substantial portion of abusers of cocaine who will use needles.

Q Is it fair to say that the vast majority of MDMA users use the drug in pill form?

A I'm sure that is certain. I would expect almost 100 percent of people, even

those who state that they -- they like to snort it. Even those people who also routinely take it orally as an ingested pill or capsule.

Q Is it true that with respect to marijuana, marijuana is typically smoked?

A In the United States, yes, it's typically smoked. Other consumption is orally, that people will eat it and swallow it; or some people are not quite smoking it but are volatilizing it. It's heated to a temperature that releases the compounds from a liquid state to gastric without burning it.

Q With respect to the vast majority of people in this country who are smoking marijuana, are there any health risks associated with smoking marijuana?

A Well, there are. The lungs are not designed for taking vegetative matter and burning it or heating it into our lungs. And so there can be changes to the physical functionality of the lungs and there has -- in the past there was concern that the smoking of marijuana is more dangerous than tobacco

because of the tars and whatnot in the cannabis. But important research tends to show -- has borne that out through the work of Dr. Tishkent, the leading expert on lung cancer.

And so it was his work -- for example, years ago people would say one marijuana cigarette has the tar of a pack or two of tobacco. And it was his work that most recently showed that marijuana did not promote lung cancer. In fact, we know that cannabis has antitumor properties. And so the extreme concerns about marijuana may be more related to those people that combine tobacco with the cannabis; because cannabis abusers tend to hold what they inhale in their lungs for a longer period of time than somebody smoking a cigarette. So if there is nicotine, if there is tobacco present when somebody is doing that, it makes the exposure to tobacco, even if it's a much smaller amount, much more dangerous for the individual.

Q What are the risks associated with inhaling marijuana smoke, including the paper

usually used to roll the marijuana into marijuana joints or cigarettes? Is that risk present in the ingestion of MDMA?

A No, because it's not -- it's not smoked or consumed like marijuana or tobacco.

Q And with respect to ingesting cocaine, as it sounds like the majority of people do in this country by snorting it or inhaling it through your nose, are there any health risks associated with ingesting marijuana -- I'm sorry, ingesting cocaine in that fashion?

A There's a number of risks because cocaine is strongly constrictive, tightening of arteries, and that can cause tissue death. That's why some people wind up having heart attacks.

Q And are those risks present, to your knowledge, with the ingestion of MDMA?

A No, I'm not aware of those risks being present. There is evidence that if MDMA somehow was being ingested chronically every single day, that it will cause alterations to heart valves. And we also believe from that

data that it is reversible when the exposure stops. It takes time for the reverse of that damage, but it should occur. But this is not a pattern of ingestion that occurs in humans.

Q So if I understand that last part correctly, any damage to the heart associated with MDMA would both be temporary and based on a use pattern that would not be likely to be seen in humans?

A That is an accurate summary of what I just said.

Q Okay. Now I want to talk about the behavior typically associated with these various drugs. Are you aware of any link or relationship between cocaine use/abuse and violent behavior?

A Yes. Cocaine is a powerful psychoactive stimulant. It can induce megalomelia behavior, narcissistic overdrive of egos -- a person believes that they are more powerful than they are -- and it promotes aggression. So, yes, cocaine abuse is associated with a higher risk.

Q Can the same be said for MDMA?

A No. The psychological effects of MDMA are not consistent with any of those that I described about cocaine.

Q Now, is there a link, in your experience or in literature, between the use or excessive use of alcohol and violence?

A It's extremely well known that alcohol is a very common associated variable to violent crime in the United States.

Q Now I want to turn back to the 2001 MDMA study that the Sentencing Commission considered. Okay?

A Okay.

Q Now, that study expressed concern that MDMA use was exploding among late teens and early adults. Is that concern still accurate today?

A That concern is not accurate. There's patterns and trends and use, and the government has done an excellent job in surveilling the country year to year to the March of the Future Studies of Johnson and colleagues out of Michigan, as well as substance work with the National Household

Drug Use Survey that they've been doing for 30 plus years. And, in fact, I believe the Department of Justice issued in 2013 a drug assessment in which the data that I just mentioned showed a decline in use year to year, since I believe the most recent data was -- in that survey was data from 2010 and 2011.

Q So if I understand you correctly, ecstasy use has actually declined between 2011 and today or perhaps between 2010 and 2011?

A I believe in 2009, according to the National Household Drug Survey, somewhere around 1.1 million people had tried MDMA, and in 2010 that reduced to roughly, I think, around 950,000; and in 2011 a little bit closer to 900,000, 920,000.

So it's gone down year to year.

Q So to your knowledge was this data available or presented to the Court at the McCarthy Hearing?

A I don't believe that specific data was presented at the McCarthy Hearing, no.

Q Is there any information offered

by the Department of Justice, in the document you were talking about, regarding the use among teenagers and young adults?

A Yes. March of the Future data focuses on surveying drug use of eighth graders, tenth graders, twelfth graders and 12 year olds also. And if I'm not mistaken, I think they quoted data that showed that youth, in general, that there is around -- close to a 4 percent reduction with use since 2010.

Q So is it your understanding at this point, if you're trying to interpret all this data, that ecstasy use has peaked?

A That ecstasy has peaked and, you know, it has gone downward before and I believe a couple of years it went up a little bit. In general, overall, it's gone down. It has gone down.

Q Okay. You mentioned earlier emergency room visits. Is there a way to obtain data regarding emergency room visits for various substances?

A Yeah. The Drug Abuse Warning

Network, DAWN, is a database, a government database that collects factors involved with emergency room visits and it's just one measure for when we look at that data, specific to drug abuse, it gives us some -- some indications of, in the real world, whether a drug is having -- has a dangerous impact on our society as theorized -- as hypothesized in some academic research.

Q And have you reviewed the most recent literature regarding emergency room visits for drug use?

A Yes, I've looked at this data.

Q Could you compare the data for MDMA emergency room admissions to the data related to cocaine and marijuana emergency room related admissions?

A Yeah. I believe looking at the DAWN data from, again, 2011, that we had about 22,000 emergency room visits, actually, for MDMA. And for cocaine it was actually a little bit over 500,000.

Q Based on your research in the field and understanding of the data, is the

difference between 20,000 and 500,000 a significant number?

A Yes, it's quite significant. In that data, for example, you know, for those emergency room data, you've got about 480,000 people showing up with marijuana. You've got 350,000 showing up for alcohol. So the fact that there are half a million people showing up for cocaine, the number one drug of abuse associated with emergency room visits that year, I'd say it is very hard to assert that cocaine is safer than MDMA.

Q Of the people, of the 20,000 people that showed up to the ER related to MDMA use, is there any way to determine how many of them were also using alcohol?

A Yes. They also will include alcohol, if it shows up. And I believe it's about 40 percent of the time that alcohol was present as well. And that's important, because we know from some basic science work that exposure to alcohol, with the presence of MDMA, increases the blood level of MDMA.

And so a person may think from

prior experience that they have taken a, quote/unquote, safe dose from their experience of MDMA, even from a pill, a set of pills that they have used previously, but in the presence of alcohol there can be as much as a 20 percent increase in MDMA availability in the bloodstream.

Q Okay. You talked about the visits related to just these drugs at the ER. Is there any way to determine or is there any measure available to determine a percentage or rate of self harm on these drugs? For example, suicide or suicide attempt rates related to these drugs?

And if that's not a clear question, I can rephrase.

A So I believe that there is such data on the -- on drug related suicide attempts, that's part of why the non-database exist. And so that ratio is calculated in the database itself and so it gives a sense of relative risk.

For cocaine it is a factor of 18.9, and with higher numbers the more

dangerous the risk. And it is not listed, though, for MDMA.

Q And what does that suggest to you, the fact that MDMA is not listed?

A That it's so rare and so -- it's statistically near zero, as opposed to cocaine, which basically, you know, is significant.

Q Thank you. I'd like to turn now to your field of research, as it stands now, regarding potential damage or changes to the brain secondary to MDMA use.

A Okay.

Q Have you heard the term neurotoxicity before?

A Yes.

Q What do you believe the definition of neurotoxicity is?

A Well, it's ill-defined and it is one of these terms used loosely in scientific literature. It's very hard to differentiate, for example, brain change from brain damage. And one of the most important ways to look for evidence of toxicity is showing that there's

some functional impact that can be associated to the use of a drug or patterns of behavior of other substances. And so -- but for me I would say probably one of the most important ways of looking at neurotoxicity would be actually neuron death, the killing of the actual cell. MDMA is not associated with killing.

Q So if we're using the definition of -- applying the definition of neurotoxicity, if we use the definition of neuron death, does MDMA have a neurotoxicity effect?

A If we're saying neuron death, the answer would be no, it does not do that.

Q Let's broaden it a bit and talk about significant cognitive impairment. Have you done any research regarding whether MDMA use at any level causes significant cognitive impairment?

A Yes.

Q Can you tell us about that research?

A Yes. I've completed one of the

largest studies ever. And the most -- really, the largest study of its kind, funded by the National Institute of Drug Abuse on removing the types of damaging compounds in the literature that exist that are highly problematic in almost all the other literature. So it was a more tightly designed study fixing the methodological failures of what existed in the literature, as well as being almost sort of a magnitude larger. It's the largest study that's completed, I believe, in the United States.

Q Okay, let me stop you there, because I want to break that down a bit.

You mentioned compounds. How would you explain that word, compound? What does that mean?

A In general, there is never a perfectly designed study. And while lawyers may pick apart this weakness, that weakness, in science we know it's virtually impossible to design a perfect study. And so those problems can be so significant as to decrease our confidence in the value of the findings.

So there's no compounds, in a sense that compounded data may invalidate the data, there's even unknown compounds, things we don't know is doing what.

But there are things that are obvious to science that would make for a stronger study, and some of these things were not attempted prior because people have assumed that it would be near impossible to do; whereas, with funding from the government we were able to importantly evaluate this question again of what's the cognitive impact of MDMA.

Q Okay. So in the interest of time, I'll ask you some more pointed questions about compounds. It sounds like basically what you're trying to do with these studies is to determine the effects of MDMA on cognitive functioning. Is that right?

A As best as we can for the study, yeah.

Q Now, it sounds like this is something that could be difficult to do. Is that fair to say?

A That's correct.

Q And is that because it's --

A Well, because the very best and most accurate way would be that you have a study subject staying within a laboratory, and then we give them a known amount of pure MDMA and we do that over time, and then we control all those factors. We know how long they're sleeping for. We know that they're not ingesting other substances. And we know that they truly are ingesting MDMA.

So using drug users from the community is less accurate than doing that. Obviously there's ethical problems with doing what I just described. So we do the next best thing. We use real world users for these tests.

Q Are there problems associated or compounds associated with questioning drug users in the community, without bringing them into a laboratory?

A There's multiple. And those problems are not addressed by the vast majority of the literature. Those problems

are inadequate control for sleep depravation. Because people who are users go to all night dance parties. And if they go and get tested while they're sleep deprived, we know that they will do worse; whereas, a comparative group of, say, college-age kids that are going to parties well rested, they wind up doing better. Not because they're free from ecstasy exposure but because they're better rested. Another would be inadequate control for other drugs of abuse, an inadequate washup period from last use.

The failure to do drug testing and the kind of neuro cognitive testing that would ensure that the person hasn't ingested MDMA in the prior three days and haven't recently used other drugs of abuse, you can do a hair analysis for drugs, to both confirm the presence of MDMA, and also the absence of other drugs, just to confirm the histories that they provided in their psychiatric interview.

Q Okay, let me stop you there.

Have other researchers tried to

control or exclude these compounds from their studies?

A As far as I know, my two studies are the only ones of the kind that addressed all of those elements.

Q And are there other studies that perhaps have -- strike that.

Is there an additional compound related to prior drug use? If we're talking about brain imaging, how would prior drug use before any involvement in the clinical study, how would that be a possible compound?

A A significant one. Because we know that the drugs of abuse do impact on -- on the brain. And so if these imaging studies, poly drug abusers, one group who have used more ecstasy than the other group or the other group is poly drug abusing and hasn't used ecstasy, that is not the same thing as evaluating somebody who's just been exposed to ecstasy, so that we can narrow it down and have a pathology to identify ecstasy. Instead, we have a question as to how much confidence do we have in these statistical

measures that are used to control for that compound.

Q You mentioned that you did one of the largest studies of this kind or perhaps the only study with MDMA that removed or accounted for these compounds. What were your results? Could you discuss your findings?

A So in a data of a couple of hundred people, all were from the dance party scene, we found no difference in cognitive performance on any of the exhaustive measures administered when we compared globally the users to the non-users.

When you do a post testing split of the data to create a group of moderate users of MDMA, those who have used it 20 to 55 times and those that are characterized as heavy users, those who have used it essentially more than 50 times, several times in their life, we do find some differences in performance, impulsivity and some other measures, like the finger tapping test.

But what's interesting is a number of them showed some trends or statistical

significance only in the moderate users, not the heavy users. And so that really reduces our concern that what we're finding is associated then with MDMA, maybe due to another factor not yet identified. But, in fact, the first study that we had published found impulsivity, and that concern is associated with the function of serotonin turnover, and we did publish on that. But then when we got -- and that's like 20, 30, 40 people, like most of the other literature out there that finds problems. But when we greatly expanded the study to a couple hundred people to peer that finding, it didn't hold.

So you can have sometimes these statistically significant findings, but it may be a function that data is compound. In almost all of the literature, you know, ten to 40 people, it may be inadequate for capturing the truth. You may find the people that are initially screened are the ones having the most problems or the most curious to volunteer for studies is a compound that you wouldn't even consider unless they're trying to get a

much larger data set, which fortunately neither would be of importance to obtain.

Q So if I understand that correctly, Doctor, you did at least two studies regarding subjects in their use of MDMA and cognitive effects. Correct?

A Yes, with relatively pure users of MDMA who had little to no exposure to other intoxicants, including alcohol.

Q Now, how did the findings -- you mentioned impulsivity and finger tapping tests. How did your findings from the first test differ from the --

A First people showed some of the measures on the -- on a test measure that actually is designed for evaluating brain trauma used prior to -- prior to our work for -- with drug abuse. But some of the measures showed an impulsive strategy in attacking the procedure of basically sorting cards and counting them in a timed fashion. But in a larger study it wasn't replicated, it did not show that. This work is relatively exclusive to users of ecstasy, and actually

was done twice by us, two different studies.

Q So based on your two studies, if we can extrapolate some conclusions from that regarding the use of MDMA, moderate to what sounds like fairly high use of MDMA, did you conclude that there is significant deprivation or significant decline in cognitive functioning, secondary to MDMA use?

A No, we did not find any ominous concerning results. We did not find anything that would support that there is a clinically significant or a functional impact on performance by those individuals who participated in this work from MDMA.

Q Was this work published in a peer review journal?

A Both were published in peer review journals. I believe the first one was published in Drug and Alcohol Dependents and the second one was published in Addiction, two of the top journals of substance abuse in the field of research.

Q Now, with respect to your second article, that was the one that was published

in Addiction. Correct?

A Correct.

Q The government has put forth before the Court an exhibit, a response to your position from -- it looks like that was also published in that journal. Have you reviewed that?

A Of course.

Q And have you replied to that, in the journal?

A Yes, we did.

Q Was the reply published?

A You know, we explained quite clearly. I mean, I can go through it point by point, if you want. But we had the last word, in a sense. None of those authors decided to try to retackle what we understood our data to show.

Q Let me stop you there, just because some of us are not familiar with the field of research in publications. A peer review journal allows responses and rebuttals. Is that fair so say?

A That's correct.

Q Okay. So there was a response to your position and that was the one that was put before the Court as an exhibit. You replied to that. Correct?

A Yes. And any legitimate fact finder has to review all of that. You can't just pick and choose what you like. You can't cherrypick. You can't just cite letters which are not -- which is not actual research, trying to pick apart our findings and then fail, utterly fail to evaluate our response to those letters. That's basically below standard, I would say, for any expert witness to do. That's just not competent work.

Q And your response was published in what year?

A It was published right alongside those letters.

Q Okay.

A So in 2011 our response to Dr. Parrot, Dr. Kish, and Dr. Rogers, are comprehensive responses to the issues that they raised, appeared right alongside their letter. So anybody who would cite those

letters and not take the time to evaluate our response is -- should call into question whether anything should be believed by that person, in my opinion.

Q Have there been any new studies involving new -- new participants, new data stats, new brain imaging, new comprehension responses is what I'm getting at, since your 2011 study involving the cognitive effects of MDMA?

A There has been one study in the Netherlands, of college kids, both prior to drug use and the years to follow. We interviewed them and then identified those people who were new to ecstasy. And so there has been some additional work published since.

Q Since you published your 2011 article?

A I believe the next MDMA data was published roughly around the same time, 2011, and then forward.

Q Doctor, are you familiar with a researcher whose last name is Parrot, in the field of MDMA research?

A Yes, I know him well.
Q And has he published anything since 2011 regarding MDMA use?
A Yes. He is often writing opinion pieces and reviews and I believe offered another review that was published in 2013.
Q I want to talk to you about that review in 2013. You've read it before?
A I have.
Q Is this review based on any new studies? And what I mean by "new," I mean after 2011?
A No, it's not.
Q Is it just a review of studies and literature that was published before 2011?
A That's correct.
Q How has that paper been accepted in the scientific community?
A Well, something remarkable and very rare has happened. The Human Psychology received for peer review a very detailed critique of Dr. Parrot's 2013 paper, completely taking him to task for that review's failure to address fully the

literature and cherrypicking over studies that would be in opposition to the points that he was raising and that had led to his miscitation and/or misdescription of other's work. That was published recently, in 2014.

MR. SCOLNICK: Okay. Before we get into that in more detail, I'm offering into evidence now what's Defendant's Exhibit B, which is your response to Parrot, Fisk and Rogers et al. I've given a copy of this to the Government.

(Defendant's Exhibit B so marked.)

Q Moving on to what we just talked about, this article that was published, critiquing or criticizing Parrot's work. I quote, Parrot's review frequently exaggerates, misrepresents or omits research findings.

Are you familiar with that provision in this 2014 article?

A Yes. And I'm stunned when reading it. Because normally -- you know, very specific language like that is reserved for an editorial or a letter to the editor, but this

actually appears within a peer reviewed article. So I took greater significance from that, especially since published in the very same journal that Dr. Parrot's 2013 review was published in.

Q Is this the latest word, this article that we're talking about here, on Parrot's research?

A I believe so.

MR. SCOLNICK: I'd like to offer, as Defendant's Exhibit C, an article entitled: A Reconsideration and Response to Parrot 2013, quote, Human Psychobiology or Ecstasy, an overview of 25 years of empirical research. And this has been provided to the Government before today.

(Defendant's Exhibit C so marked.)

Q Do you agree with the conclusions of this 2014 article?

A I do.

Q There have been a number of studies that have found some brain changes relating to MDMA. Correct?

A Correct.

Q And to summarize your understanding of the state of the field right now, is there any research, reliable research or findings that have confirmed significant cognitive impairment secondary to ecstasy use?

A I'm not aware of any research that shows clinically meaningful impairment from MDMA abuse.

Q Could you explain that, what do you mean by clinically -- significant, I think you said?

A Clinically meaningful. So something that can take on statistical significance. The fact that a person may perform a few milliseconds to a few seconds slower than somebody else may take on a statistical significant study, that the difference between the two really identifies one group over the other. But that -- but both measures, both results could be in the functionally normative range of performance.

So merely finding that we have a statistical significant decrease in

performance is insufficient to take away a message that MDMA will damage your performance in everyday life.

Q I only have a few more questions. We need to turn it over to the Government to give them an opportunity to question you here. But regarding these findings, the clinically insignificant decrease in performance.

Are there any other drugs, legal, either by over-the-counter or prescription drugs, that have a similar effect; meaning, decrease in performance to MDMA?

A Yes.

Q Could you explain what those drugs are?

A Well, for example, much has been claimed that MDMA use may cause verbal memory deficits, with other measures of how we access language. And we already know that Vicodin, Clonidine, those sorts of drugs, all of them do that. All of them can cause verbal memory deficits. In other words, if we're concerned about, like I said, neuron death, alcohol causes neuron death. I don't know if I can

clarify that, but MDMA does not cause neuron death.

Q Now, comparing MDMA to alcohol, would you say that alcohol causes significant -- significantly more brain damage than MDMA?

A Well, having done a different study, looking at the long term neurocognitive functional consequences, in this case its comparison of those who follow the native American church. One of the comparison groups was native Americans who had been daily heavy drinkers of alcohol and were now sober. And there has been extensive and exhaustive literature showing significant cognitive damage from alcohol, all of which is nowhere near realized in any of the data for MDMA. It's just remarkably damaging to cognitive function when a person is pathologically addicted to alcohol.

Q Thank you. Just one other area.

In 2011 the judge in the McCarthy case was concerned about the fact that MDMA was, I believe the quote was, aggressively

marketed to children and young teens. I might be misquoting it, but that was the idea.

Do you think that that concern is still a valid one at the present time?

A Well, marketed, you know, how and by who? Since 2011 electronic dance music has become more popular. Some of that music has messages of drug use. It's quite typical in pop culture to include the use of MDMA. But that's not marketing specific to entice people to use, you know, by drug dealers.

But separate from what's popular in entertainment, I would say no, it's not aggressively marketed, if -- or it's ineffectively marketed. Because as we started out with -- with earlier questions, we have government data showing that use has decreased, not increased.

Q And in your experience dealing with teenagers or young adults who are abusing MDMA, is it your experience that they have used marijuana at the same time or prior to using MDMA?

A It is quite common that people

will have abused multiple drugs. The consumption of alcohol from the age of 21 is also an elicit activity. It's to be expected that most youth will have broken the law and gotten intoxicated with alcohol as well. So, yes, since marijuana is the most abused elicited substance, other than alcohol, it would be common to expect that they've also been smoking marijuana.

MR. SCOLNICK: Thank you. And then just before we finish, I want to admit as Defense Exhibit E, the study discussed from Scotland which is entitled: Quantifying the RR of harm to self and others from substance misuse: Results from a survey of clinical experts across Scotland. That was the article --

THE WITNESS: I'm sorry, I forgot, yeah.

MR. SCOLNICK: Okay. And with that, I turn it over to the Government.

(Defendant's Exhibit E so marked.)

EXAMINATION BY MS. MOORE:

Q Good morning.
A Good morning.
Q I just want to clarify a couple of matters you discussed with Mr. Scolnick.
You mentioned emergency room visits. Were the numbers that you gave us total visits? For instance, the 22,000 for MDMA, that would be total emergency room visits?
A This is looking at the most recent non-data that was published, yeah. So this is from --
Q To total reported visits?
A -- 2011, drug related emergency department visits.
Q Those were the total reported visits?
A Total reported visits to the emergency room department for any elicit drug for that year was ranked at 1,252,000.
Q Okay. And then for each of the drugs, the number of visits that you gave us was just the total visits not a percentage of users of that drug who had visited the E.R.

Correct?

A There is both the wrong number of emergency department visits, as well as a percent of E.D. visits. The numbers that I was using was the number, not the percent.

Q But the percent you're talking about there, is the percent of total emergency room visits for one particular drug, not percentage of users of a drug who end up in the emergency room. Correct?

A That's correct. In order to do that, what we could do is look at the National Council Survey data of total users estimated in the country, and then we could factor in the number of emergency room visits to that number to get an estimate of how many users overall wind up in an emergency room. And I believe that number would be quite small for MDMA in comparison to cocaine.

Q Do you have that data?

A The government doesn't publish data that crosses it. I actually have chapters I wrote. I think I actually did do that comparison. It's not at my finger tips.

But I remember from my numbers that I just described, that MDMA was much, much lower than cocaine.

Q You mentioned before, when you were discussing cocaine, powdered cocaine versus crack cocaine, when you were discussing cocaine more broadly during your discussions with Mr. Scolnick, was your use of the word cocaine exclusive to powdered cocaine or was it including both: The powder and the crack?

A It included both.

Q I'm sorry, I couldn't hear you?

A Yes, both.

Q So every time you talked about the harmful nature of cocaine, you're talking both powdered cocaine and crack cocaine?

A That's correct. They're both of a significant greater risk, in my opinion, than MDMA, whether you separate them or not.

Q Turning to your 2011 study. The median lifetime uses of MDMA in your study was 43.5. Right?

A Correct.

Q And are you aware that other

studies have suggested that MDMA users take approximately 200 tablets over a lifetime. That's average?

A That's the number of instances of MDMA ingestion, that's not the number of pills.

Q Do you have a number for average use of pill usages?

A If you give me a second I can give you that data. I'm still looking for my actual paper. So data published in 2011 just offered the number of separate instances. The median number of pills, I'm fairly certain it was over 100 pills. I'm looking to see if it's also in our response to Dr. Parrot. I'm not finding it. But it was significant. It was certainly of a similar magnitude of pills, especially heavy users.

Q Okay. That's fine.

A I'm sorry. I believe our largest user had ingested MDMA on more -- with more than 400 pills.

Q Okay. Are you aware that Kish published a study in 2010 and found that MDMA

results in toxic outcomes to serotonin neurons within the cortex and hippocampus among other areas?

A I'm aware that Kish -- that the Kish 2010 imaging study have, yes, decreased. But importantly, unlike what was found on McCann in 1998, there is an official serotonin transporter throughout the brain and that's in the very same paper that you cited. And then if you turn to some of the other researchers that show that sert can rebound over time because there's a very large range in the sert binding. So, again, what's -- the fact that there's a declarant like that found is enough to serve that its of clinical importance with some drugs that do much the same that are -- that are actually approved.

Q Okay. Were you aware that McCann published a 2008 piece that found a correlation between reduced sert binding and neurocognitive deficit in MDMA user's maintenances?

A I am aware of that paper but we also know that sert binding detriments are not

permanent.

Q Okay. Are squirrel monkeys closely related physiologically to humans with regard to metabolizing MDMA?

A We know that using monkey primates is for clinical, for preclinical research is going to give more, in general, more accurate data for us, and that the metabolic -- the metabolism of MDMA in nonhuman primates is going to approximately give a use.

Q Okay. And are you aware that in testing the effects of a single oral dose of MDMA, Cowan et al in 2007 found that it produced a significant dose related depletion of serotonin and metabolite 5-HIAA in the cerebral cortex, hippocampus, and thalamus of the squirrel monkeys?

A Sure. Using doses that might not scale to human, because we wanted animals to actually give a dose that will achieve a toxic finding. But that doesn't mean that it is consistent with what most humans do in their abuse of the drug. And also it's -- what's of interest is what happens over time. We could

survive acute exposure of the brain to a substance that's going to alter brain function and brain chemistry during testing. During that acute phase it's most likely to realize detriments in performance and detriments in brain measures such as that. But what happens over time, what's the functional significance of that? That's the more pressing question, in my opinion.

Q Okay. Well, are you aware that in 2010 Kish published a study examining users of approximately 200 lifetime doses of MDMA and found that there is an inverse relationship between the length of MDMA use and sert binding reduction?

A I'm aware of his findings. I'm also aware that Dr. Kish is -- I mean, I hate to put words into his mouth. Let me just be accurate about this. Kish is not raising red flags that we've got a dangerous and neurotoxic drug in MDMA even from his 2010 findings. Maybe Dr. Parrot is somebody who likes to cherrypick like that. But no, even Dr. Kish does not validate that conclusion and

nowhere does any physician say that it is as dangerous as cocaine. So it's very concerning. It's a very concerning thing.

Q Are you aware that this study identified deficits including -- and forgive me, I'm probably going to pronounce this wrong -- serotoninergic neurotoxicity?

A Well, fortunately it doesn't do the neurotoxic thing that alcohol does of actually killing brain cells. So what we call reformation of detriment extending from serotonin after exposure from MDMA to be, quote/unquote, neurotoxic if you want to do that. But those very same changes in monkeys, in humans, were well known by FDA when they considered and approved the drug phenformin, which was at market. So those very changes that you're describing right now have in the past been considered by the FDA and they still went ahead and approved the drug any way.

Because when you have known medical benefits for a drug, you can also give a form of consent that there may be some problems. There's many drugs that cause some

inherent cognitive function. If you're dying of brain cancer and I give you a highly toxic dose of chemotherapy that gives you five more years of life but shaves five points off your IQ, I bet you take it.

We're not going to prevent you from having that life-saving drug even though it may impact your cognitive performance. We have a drug that doesn't have any supplemental utility. Any of these findings from a clinical perspective can be milked by those who want to lie to the public in asserting that actual MDMA is a greater danger to our public health than cocaine.

Q Are you aware that Jacobsen, in 2004, showed that MDMA users had demonstrated abnormal function of the hippocampus during memory function tests?

A I would need to see that actual paper just to refresh my memory. I'm sure what we're looking at, all these studies with tons of compounds in them, in a control for past drug use and incentivized that's rather small in making it very difficult to

extrapolate risk for the public at large. But sure, I'm -- I would expect that there can be such findings, yes.

Q Okay. And are you aware that Von Geusau, in 2004, also showed significantly worst performance of male MDMA users on task, that correlate to cognitive flexibility and on the combined executive function test?

A Yeah, and that's an example of the type of weak literature that exist. Why we were funded to do the work that we did. You know, obviously if I had just found more harm, it would have been great for me to get more funding to just continue to do that. But I just honestly published my findings that we had. But small studies like the one you just cited are not of significant value compared to my own published work.

Q All right. Are you aware that Jager, in 2008, found using the FMRI, that MDMA was associated with reduced associative memory performance?

A Again, there are multiple compounds in that work that show they were

removed to have real confidence. That what we have is a finding of public health consequence. It's concerning, there's no doubt about that. But what's the functioning take home message from it, is it's still controversial. And the fact that this controversy has remained for such a long time points to the weakness of the underlying argument that MDMA is the clear and present danger as being attempted by the government still, and quite sadly.

But it's important for -- I mean, put it this way: I have yet to interview a single drug user that thinks that a drug is safe. No user thinks that. But this message is being promoted that if we talk about relative risk then we may be assuring safety to some people. I have never, I have never once said that MDMA is safe. I prefer that people don't abuse drugs, including MDMA.

Since we're in a world where people can still obtain them, we have to accept that some drugs are going to be more dangerous than others and it would be wise for

us to target those drugs that are doing the most damage to our society, which we're not quite doing.

Q Are you aware that according to NIDA, affects of acute or short-term cocaine use are usually reserved to clinical symptoms?

A I didn't hear the second part. Are usually what?

Q Reserved to clinical symptoms.

A I'm not sure what you're saying.

Q Such as tachycardia or seizures or increased blood pressure, things like that.

A Or as I described, you know, having a heart attack also causes cognitive deference in performance, in carrying oxygen to the brain. So from a medical standpoint as a physician, we can -- what we care about are the actual people and whether the risk is directly related to the drug or indirectly related through the pattern of abuse. In the end it's still harming the same person.

And when we look at that real world situation, there's not a single physician I know of who would ever agree with

the government's position or the U.S. Sentencing Commission's position that cocaine is a substantially safer drug from MDMA. This may be one of the most dangerous public health messages that the government is allowing to continue to stay.

Q Are you aware that taurine is a neuro-protective amino acid that reduces the excitatory actions of the brain and protects against -- excuse me, I'm probably pronouncing this wrong -- dopaminergic neurons?

A Dopaminergic neurons, yeah.

Q And are you aware that Yablonski-Alter, in 2009, found that while neurophysiological changes can begin to occur following continued use of cocaine, repeated cocaine administration also results in the release of taurine?

A Which that points out to just how toxic cocaine is since we see victims of stroke induced from cocaine and from people after their heart attacks, that the brains aren't functioning like they used to. That points out even more how dangerous cocaine

must be that it can release something neuro-protective and yet we see clinically all the time these severe damages from cocaine never, never seen on a routine basis like cocaine with MDMA. It's really sad.

Q Were you aware that subsequent cocaine use has been shown from Nestler, in 2005, to result in an increase in dendrites?

A I guess that would be an example of neurotoxicity. Right? Because that's brain change. You can't just cherrypick and say that the reformation of dendrites from neurons, MDMA, causes brain damage when you're now citing a paper.

So to repeat myself, if we follow the logic that alteration of the expression of dendrites from MDMA is, quote/unquote, neurotoxic, then the alteration of dendrites from cocaine to increased expression of dendrites, this too must be an example by that definition of neurotoxicity.

Q Turning to the paper that you spoke with Mr. Scolnick briefly about, it's titled: The Reconsideration and Response to

Parrot, best beginning of it.

Are you aware that the authors of this piece listed a conflict of interest in their paper?

A Yes.

Q Because two of the authors are affiliated with MAPS as the executive director and as a clinical research and information specialist. Right?

A Yes, I'm aware of that.

Q And are you aware that developing MDMA into an FDA approved prescription is MAPS top priority?

A I can't speak to their -- their direct agenda or top priority, since I'm not a member, a person who is running MAPS or anything like that. I'm not a MAPS researcher.

Q Are you aware that that is something that MAPS is interested in, whether or not --

A Oh, yeah, of course. Of course.

Q And then turning to the Nut piece. In that article you're aware that the

researchers discussed the limitations in their papers. Right?

A All good studies should do that, yes.

Q And in this paper the authors noted that many of the harms of drugs are affected by their availability and legal status, which varies across countries. So our results are not necessarily applicable to countries with very different legal and cultural attitudes to drugs. Right?

A Well, you know, it's nice to see a discussion that includes such a statement. But the fact is, is that Great Britain is a member of international psychotropic treaty, just like the United States, and is subject to the same international conventions as the United States for the control of drugs listed as, you know, Schedule I in the United States, Schedule A in Great Britain. And there is a significant overlap in our western societies. So it's -- it's doubtful that such a concern would be of significant relevance as here in the United States.

Q Okay. And the researchers also noted there that a low score in their assessment didn't mean that a drug wasn't harmful. Correct?

A Absolutely, that's correct. Absolutely, that's true.

Q All right. I have --

A Nobody should take that message that a drug is safe. There's no drug that's safe.

MS. MOORE: All right, thank you. I don't have any more questions.

EXAMINATION BY MR. SCOLNICK:

Q Just a couple further questions, Doctor.

The government discussed with you a number of studies. It sounds like those studies occurred between 2004 and 2010. Is that right?

A I believe so. A number of them were.

Q Well, we talked about Kish, McCann, Jacobsen, Jager, Von Geusau?

A Yeah, yeah, that's right.

Q All of this information was available before 2011. Right?

A That's correct.

Q And these aren't the only studies in the field of MDMA cognitive research, are they?

A No, there's thousands of papers on MDMA.

Q And are there a number of studies that agree with your findings?

A There are a number of studies that agree with our findings. The work of Gill and Magetty was published, I think, subsequent to my work. And Dr. Michael Laverse from Australia has published some evidence similar. And there have been other groups as well that have done some -- some overlap with the results that we report, but none of them are with the number of individuals or the control for the compounding variable that I mentioned quite like the work that was published in 2011, which I believe still should be considered the standard reference by which we should look at this question, although

controversial, of what happens when people who abuse MDMA and their cognitive performance.

Q And with respect to the issue of significant cognitive impairment, secondary to MDMA use, what is your opinion and conclusions of the vast majority of MDMA researchers?

A That there are some findings that are -- that raises concern and warrant continued investigation, as well as surveillance of those who are MDMA users. But it remains controversial to assert one physician over the other as still enough basic and clinical research to point to some deference in performance which are not, right now, found to be of significance but that's still hurtful. It needs to be looked at.

But there is no data that is supportive of identifying MDMA as being a concerning drug to people's cognitive functioning nor is there data to warrant at this point the assertion that MDMA is more dangerous than cocaine or that MDMA is even an equivalent danger to MDMA. So we have a tremendous amount of data showing that cocaine

is indeed more dangerous than MDMA.

I don't know any doctor that would oppose that statement about MDMA versus cocaine. Not a single physician could, have I ever found, and I ask this a lot, that finds cocaine safer than MDMA. It's just absurd to ever proffer such a conclusion at this point of what we know, both clinically and in scientific literature. That is conclusive.

(Continued on the next page.)

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

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

ERRATA SHEET

PAGE/LINE	CORRECTION

ERRATA SHEET

PAGE/LINE	CORRECTION

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.

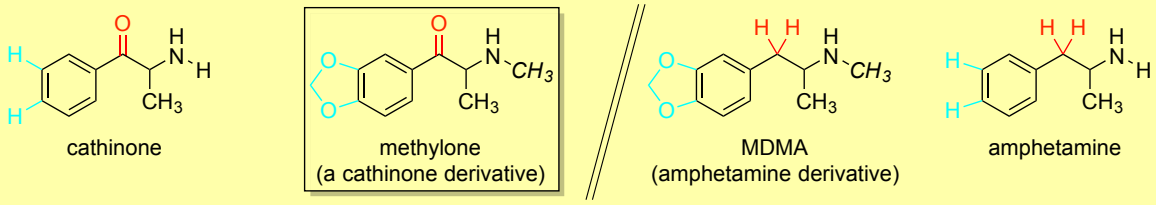
6. I am an organic chemist with professional expertise in synthetic chemistry, chemical structure, molecular interactions, and structure-activity relationships. My primary research focus is on the synthesis of drugs and drug-like compounds. I have published and lectured extensively in these areas, as 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.

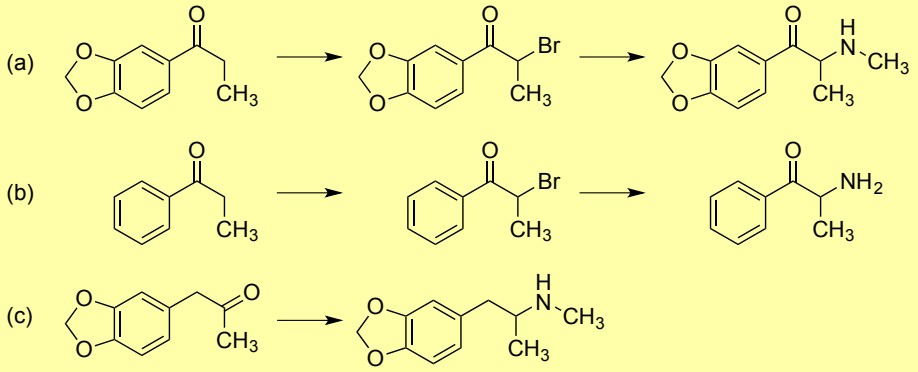
12. In contrast, methylenedioxymethamphetamine (MDMA) is classified as an “amphetamine” because MDMA has the amphetamine core structure.

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).

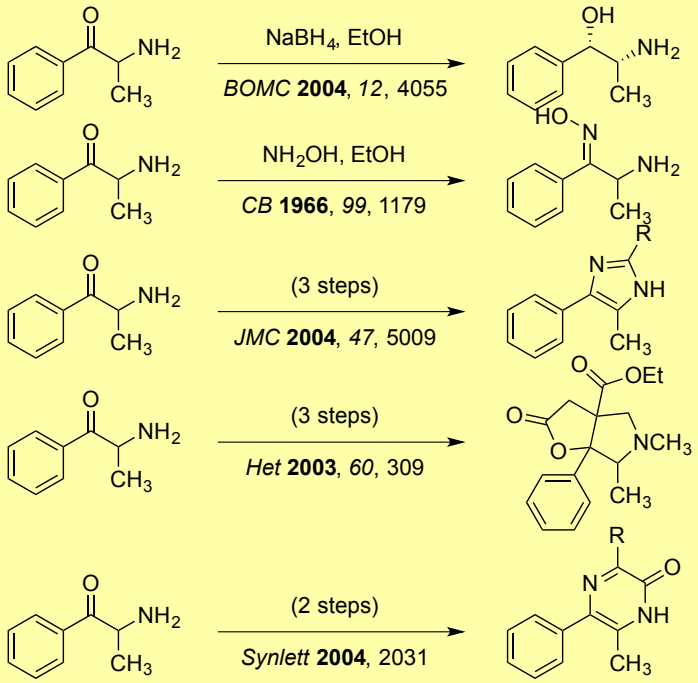
19. The syntheses of cathinone and methylone follow similar paths, whereas the synthesis of MDMA is different.

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.

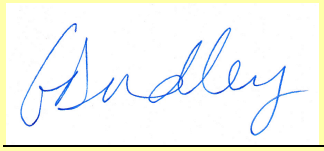
27. Cathinones and amphetamines both have amines (nitrogen groups), but only cathinones have the ketone (C=O) group, which opens up a much larger set of chemistries.

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.



GREGORY B. DUDLEY, Ph.D.

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-methlenedioxymethamphetamine (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 existenial 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-methylenedioxypyrovalerone), 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 momoamine 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, buproprion, 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 polysubstancEx. 1, N.Y. Hrg. Tr. at 382 (Hanson).e 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,

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.

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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.

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-methlenedioxymethamphetamine (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 existenial 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-methylenedioxypyrovalerone), 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 momoamine 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, buproprion, 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. 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

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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.

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Executed on June 21, 2014 at Irvine, California.

CHARLES S. GROB, M.D.

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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.

Executed on June 21, 2014 at Irvine, California.

CHARLES S. GROB, M.D.

CURRICULUM VITAE

Charles S. Grob, M.D.
Department of Psychiatry
Harbor-UCLA Medical Center
1000 West Carson Street
Torrance, CA 90509

PERSONAL DATA:

Born: August 14, 1950
Birthplace: Baltimore, Maryland

EDUCATION:

1968-1971 Oberlin College
1973-1975 Columbia University (B.S. 1975)
1975-1979 State University of New York, Downstate Medical Center (M.D. 1979)

CLINICAL TRAINING:

1979-1980 Internal Medicine Internship, Pacific Medical Center, San Francisco, CA
1980-1983 Psychiatry Residency, Cedars-Sinai Medical Center, Los Angeles, CA
1982-1983 Family, Child and Adolescent Psychiatry Fellowship, Cedars-Sinai Medical Center, Los Angeles, CA
1983-1984 Child Psychiatry Fellowship, The Johns Hopkins Hospital, Baltimore, MD

ACADEMIC APPOINTMENTS:

1984-1985 Instructor, Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD
1985-1987 Assistant Professor, Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD
1985-1987 Assistant Professor, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD
1987-1993 Assistant Professor, Department of Psychiatry and Human Behavior, University of California Irvine, College of Medicine, Irvine, CA
1993-1999 Associate Professor, Department of Psychiatry, UCLA School of Medicine, Los Angeles, CA

1995-1999	Associate Professor, Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA
1999-	Professor, Departments of Psychiatry and Pediatrics, UCLA School of Medicine, Los Angeles, CA

CLINICAL POSITIONS:

1984-1987	Director, Adolescent Psychiatry Service, The Johns Hopkins Hospital, Baltimore, MD
1984-1986	Medical Director, Psychiatric Services, John F. Kennedy Institute School, Baltimore, MD
1986-1987	Coordinator, Child Psychiatry Teaching General Psychiatry Residents, The Johns Hopkins Hospital, Baltimore, MD
1987-1993	Director, Adolescent Psychiatry Unit, University of California Irvine Medical Center, Orange, CA.
1991-1993	Acting Director of Education, Department of Psychiatry, University of California Irvine Medical College of Medicine, Irvine, CA
1991-1993	Director, Residency Training, Department of Psychiatry, University of California Irvine, College of Medicine, Irvine, CA
1992-1993	Director, Medical Student Education in Psychiatry, University of California Irvine, College of Medicine, Irvine, CA
1993-	Director, Division of Child and Adolescent Psychiatry, Department of Psychiatry, Harbor-UCLA Medical Center, Torrance, CA

SPECIALTY BOARDS:

1984	Board Certified, American Board of Psychiatry and Neurology - Psychiatry
1986	Board Certified, American Board of Psychiatry and Neurology – Child Psychiatry

PUBLICATIONS:

1. Grob, C.S.: Single Case Study: Female Exhibitionism,: Journal of Nervous and Mental Disease, 173:253-256, 1985.

2. Grob, C.S.: Persistent Supersensitivity Vomiting Following Neuroleptic Withdrawal: A Case Study in an Adolescent, Biological Psychiatry, 21:398-401, 1986.

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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.

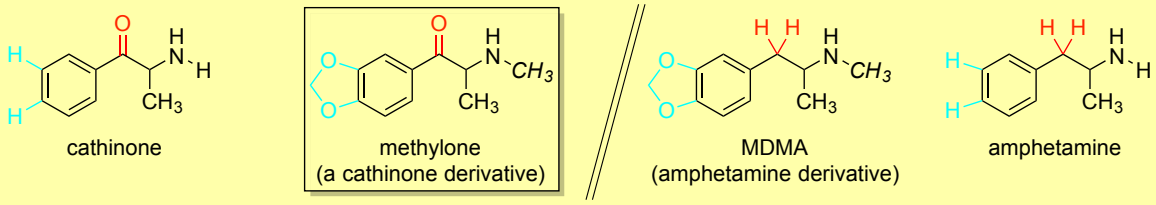
6. I am an organic chemist with professional expertise in synthetic chemistry, chemical structure, molecular interactions, and structure-activity relationships. My primary research focus is on the synthesis of drugs and drug-like compounds. I have published and lectured extensively in these areas, as 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.

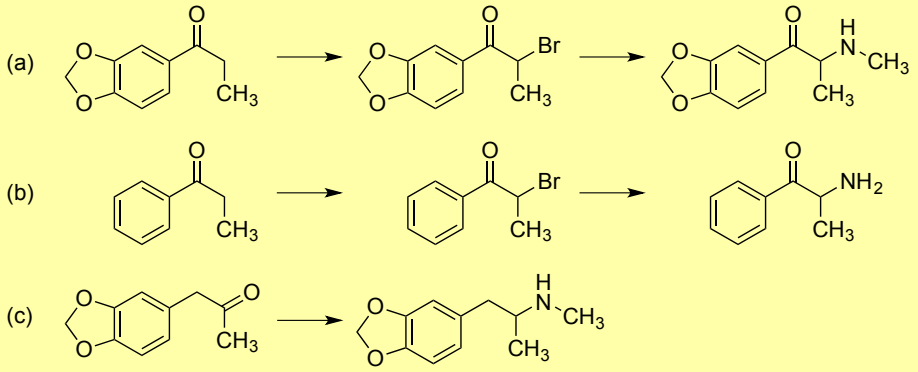
12. In contrast, methylenedioxymethamphetamine (MDMA) is classified as an “amphetamine” because MDMA has the amphetamine core structure.

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).

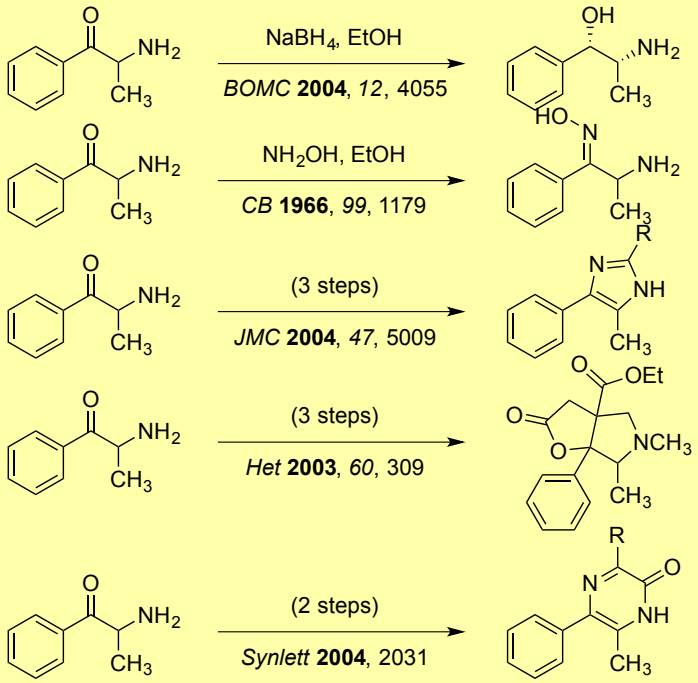
19. The syntheses of cathinone and methylone follow similar paths, whereas the synthesis of MDMA is different.

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.

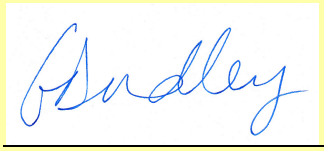
27. Cathinones and amphetamines both have amines (nitrogen groups), but only cathinones have the ketone (C=O) group, which opens up a much larger set of chemistries.

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.



GREGORY B. DUDLEY, Ph.D.

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 "methylone" 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. Methylone and MDMA are believed to be transporter substrates, while evidence indicates that cocaine is a 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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PROBATION OFFICERS ADVISORY GROUP

An Advisory Group of the United States Sentencing Commission

February 21, 2017

United States Sentencing Commission
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Dear Commissioners,

The Probation Officers Advisory Group (POAG or the Group) met in Washington, D.C., on February 8 and 9, 2017, to discuss and formulate recommendations to the United States Sentencing Commission (USSC). We are submitting comments relating to issues published for comment dated December 9, 2016.

1. FIRST OFFENDERS/ALTERNATIVES TO INCARCERATION

First Offenders

The First Offender Amendment garnered much discussion amongst the members of POAG. While the idea of conferring a benefit to those offenders who pose the lowest risk of recidivism was generally agreed upon, the practicality of defining who falls into this "first offender" definition proved rather difficult.

The majority of the members favored Option 1, which suggested a decrease of one level from the offense level determined under Chapters Two and Three. This approach was favored because it was similar to the upward departure from category VI directive under USSG §4A1.3(a)(4)(B) where the departure is structured by moving incrementally down the sentencing table. It was believed that this option provided a way around the prohibition of a departure from Criminal History Category I by resulting in a reduced offense level as if there were a Criminal History Category 0. While the idea of creating, in essence, a Criminal History Category 0 was pleasing, POAG had concerns about how to appropriately define a "first offender."

POAG was unable to reach a consensus as to the criminal history characteristics of a first offender. While some agreed that a defendant who does not receive any criminal history points under Chapter Four, Part A, and has no convictions of any kind is a "first offender," others favored a stricter adherence to the definition of the term wherein a defendant with any criminal history, including an adjudication, arrest, or infraction, is disqualified from the adjustment. Given the variety of reasons for the dismissal of criminal charges, it was believed by some that a defendant with several law enforcement contacts, despite having no convictions, is not the quintessential first offender. Additionally, it was believed that there may exist unintended consequences and disparate application of the adjustment. First, the consequences for certain minor offenses, including driving with a suspended license, vary greatly by state and can involve either criminal or civil punishments. As such, a defendant's civil punishment for these minor offenses, despite not being attributed criminal history points, could be considered a "conviction" resulting in the defendant being precluded from the adjustment. Second, POAG recognized that defendants of lower socioeconomic status and/or minority populations are often subject to more police presence in their neighborhoods which increases the likelihood of sustaining convictions for minor offenses resulting in them being precluded from the adjustment more often than the typical white collar or even child pornography defendant.

POAG discussed whether the nature and the duration of the instant offense should be a factor in the determination of a first offender. For example, should a defendant who commits a firearms-related offense or who commits a tax fraud over a prolonged period of time involving the submission of several fraudulent tax returns be considered a first offender? Given the complexity of establishing an elements-based analysis for a first offender and the need to simplify guideline applications, it was agreed that criminal history should be the determinative factor in deciding who is a first offender and that the nature and duration of the offense should be considered in determining the application of the rebuttable presumption for a non-custodial sentence at USSG §5C1.1. POAG believes the severity and/or the extended duration of the offense should not bind the court to the presumption of an alternative sentence and that it could impose imprisonment in those cases.

Alternatives to Incarceration

POAG appreciates the Commission's continuing work to expand the use of alternatives to incarceration within the structure of the guidelines. POAG has encouraged the Commission to adopt a bifurcated Sentencing Table that expands the availability of probation-only sentences. POAG stands by this proposal and believes this cost-effective alternative is under-utilized within the present framework. The Federal Probation system provides national leadership in its approach to risk-based supervision – tailoring higher intensity interventions for high risk cases. However, POAG has concerns that the well-intentioned Zone B/C consolidation will lead to longer terms of location monitoring (LM) for low risk cases that may result in a higher rate of negative supervision outcomes.

As POAG discussed in its two previous papers, there is a legitimate concern that longer terms of home detention with LM in low risk cases will ultimately run afoul of the "risk principle" and actually reduce successful outcomes. POAG argues that LM should be imposed mindfully, to address specific risks and needs, rather than being imposed in a blanket fashion to everyone within a particular guideline imprisonment range. Anecdotal feedback from officers in the field is strongly critical of home detention terms that exceed six months. It is a very restrictive intervention that can impact the mental health of those under supervision, and the longer someone is subject to LM, the more likely they are to test the limits of the equipment.

Officers responsible for LM supervision have a number of policy requirements to meet in all cases. Monthly home contacts are required to examine the equipment and officers must respond to certain key alerts during the day and night – expanding the range of non-traditional working hours. LM officers are responsible for verifying the activities of offenders outside their homes and must review geo-locational data for all offenders enrolled in GPS systems. In short, individuals sentenced to home detention with LM receive resource intensive supervision consistent with that of a sex offender or violent recidivist.

Location Monitoring Specialists are known to experience high stress levels/burnout due to the nature of their work and the national system has dedicated resources to provide education on officer wellness. POAG is concerned the proposed amendment will embolden courts to impose long terms of LM in a blanket fashion more often – significantly adding to the overall workload of LM officers and taking resources away from the true high-risk cases that deserve the most intensive supervision.

POAG encourages the Commission to exercise caution in its approach to this proposal and instead seek to expand probation-only dispositions rather than authorizing lengthy terms of home detention with LM. At the district court level, probation officers work hard to educate judges and attorneys about the most effective use of LM, and POAG hopes that the Commission can strike a balance that expands the use of probation without overly relying on home detention as the vehicle to achieve that end.

2. TRIBAL ISSUES

The proposed amendment incorporates recommendations from the Tribal Issues Advisory Group (TIAG) regarding the use of tribal convictions to compute criminal history scores under Chapter Four and how to account for protection orders issued by tribal courts.

POAG concurs with TIAG's recommendations and the Commission's proposed changes to the guidelines for consideration of tribal convictions. The convictions should not be assessed criminal history points under USSG §4A1.1, and should remain under USSG §4A1.2(i). POAG recognizes procedures may vary among the many tribal courts. Due process issues and lack of documentation of tribal convictions are a concern and impact the correct assessment of criminal history points.

The policy statement under USSG §4A1.3 (Adequacy of Criminal History) will continue to provide a means for the court to grant departures based on information available regarding tribal convictions. Additionally, important changes have expanded the jurisdiction of tribes in criminal prosecution (i.e. Tribal Law and Order Act of 2010 and Violence Against Women Reauthorization Act of 2013). POAG concurs with the proposed commentary under USSG §4A1.3, comment. (n.2(C)(i) –(iv)) and agrees this provision will provide clear guidance. However, POAG recommends that (iv) be expanded to include language to also allow for a departure if the defendant was under tribal court post-conviction supervision at the time of the federal offense, similar to the application of USSG §4A1.1(d). POAG believes there will be difficulties with practical application of USSG §4A1.3, comment. (n.2(C)(v)) in determining if the tribal government has "formally expressed" a desire for the convictions from the tribal court to be used for computation of criminal history points. It is unclear who determines this formal expression, how it is determined, and how it will be documented. The definition of "formally expressed" may lead to additional disparity because the procedures vary among tribal courts. POAG believes (v) could be eliminated from the list because (i)-(iv) provide sufficient guidance.

POAG concurs with the recommendations of TIAG and the Commission's proposed language to define "court protection order" under USSG §1B1.1, as it will provide consistency with statutory definitions.

3. YOUTHFUL OFFENDERS

POAG discussed the amendment on whether the Commission should consider changing how the guidelines account for juvenile sentences for purposes of determining the defendant's criminal history pursuant to Chapter Four, Part A. Specifically, to amend the guidelines to provide that sentences resulting from juvenile adjudications not be counted in the criminal history score.

After a lengthy discussion, POAG was unable to reach a consensus on this issue. Those in favor of the amendment cited disparity, both curable and incurable, as the primary reason for change. This includes the wide range of varying access to juvenile records, from state to state, as well as jurisdiction to jurisdiction. While some locations have relatively easy access, in others access is non-existent. This is based on records being sealed or destroyed, while in other locations the length of time to obtain records was problematic. It was also discussed how the search for juvenile records is inefficient and costly as it relates to our daily work formula, specifically in relation to time and resources. POAG also noted the frequent inability to obtain records from other states via our system's "collateral" process, which POAG agreed is not reliable or consistent within our own system. POAG also cited the many differences in how juvenile offenses of a similar nature are treated from state to state. POAG generally observed that the issues above, along with inconsistent scoring of juvenile adjudications, lead to certain disparity between offenders from court to court.

Those who were in favor of no longer scoring juvenile offenses were in agreement of then having these adjudications considered for purposes of an upward departure under USSG §4A1.3. The group also did not agree to count juvenile sentences only if the offense involved violence or was otherwise serious, citing recent debate with the definitions of these offenses.

Chapter Four, Part A – Criminal History was designed to quantify prior criminal behavior by a defendant from those defendants without any criminal behavior history and as noted in the Introductory Commentary, "a defendant with a record of prior criminal behavior is more culpable than a first offender and thus deserving of greater punishment." Currently all juvenile status offenses and truancy are not scored pursuant to USSG §4A1.2(c)(2). All other juvenile sentences are counted only if the sentence imposed was done so within five years of the defendant's commencement of the instant offense. Those opposed to the proposed amendment indicated this five-year recency provision captures and accounts for only those juveniles who have a higher likelihood of recidivism and future criminal behavior based upon their criminal past. Accounting for past criminal behavior is especially important given that our system is seeing more violent and repeat young offenders than in the past. Any minor behaviors (those captured in USSG §4A1.2(c)(2) and those stale (beyond the five-year point)) have already been excluded based upon these other provisions.

POAG members in opposition to the proposed amendment also commented that historically juvenile offenders receive graduated sanctions where they are often offered initial leniency from the juvenile courts and more serious sanctions were only imposed upon new, repeated or more serious behaviors. Given this pattern, the scoring of juvenile adjudications within five years would continue to identify those juveniles who have committed recent and more serious, or escalating behaviors. To not score or account for the adjudications would be essentially "turning a blind eye" or treating juvenile offenders equal to those individuals with no juvenile criminal past, thus promoting disparity. The scoring of juvenile adjudications distinguishes those who became involved in the juvenile system from those who were law abiding. If juvenile adjudications were ignored in the scoring system, the young offenders' risk of recidivism and potential harm to society would be underrepresented because their pattern of juvenile criminal conduct would be unaccounted for in the sentencing guideline scheme.

Obtaining juvenile records in some jurisdictions and not in others, thus creating unintended disparity, is also concerning to those in opposition to the amendment. This concern, however, is not outweighed by the need to punish those who demonstrate repeated criminal behavior.

4. CRIMINAL HISTORY ISSUES

POAG discussed the proposed change to USSG §§4A1.2(k) and 4A1.3 (Revocations and Downward Departure). POAG members were unanimous that revocations of supervision should be counted toward a defendant's criminal history, and therefore, not considered as a departure under USSG §4A1.3. Several areas of concern were discussed. Although there may be multiple terms of supervision, the application of additional points for the violation is limited to one case, which prevents double counting. This application has been included in the guideline since its inception and the need for change is not apparent. Under the amendment, a potential exists for not capturing the more serious (higher risk) defendants who have failed to comply and thereby affording them the same benefit as offenders who have successfully completed prior terms of

supervision. Additionally, for those individuals who initially received a supervisory sentence, with the four-point cap under USSG §4A1.1(c), there is a likelihood that their noncompliance, which may not include recidivist criminal conduct, but instead serious technical violations, would not be considered. Currently under USSG §4A1.1(d), points are assessed for committing the instant offense while on supervision. This same logic should be applied to assessing points for violations.

Regarding the proposed amendment for a downward departure in a case where the actual time served is substantially less than the length of the sentence imposed, POAG expressed a concern with the inconsistencies which may occur based on jurisdictional computations. As previously discussed by POAG members, there are a number of issues with determining why the "time served" and the "time imposed" varies. Some of the controlling factors are unrelated to the defendant and the offense of conviction, and therefore, should not be a consideration for a departure.

5. BIPARTISAN BUDGET ACT

POAG members noted that they have very little experience with this statute given it is a fairly new law. However, POAG members did favor the reference to 42 U.S.C. § 408(a), § 1011(a), or § 1383a(a) at USSG §2B1.1(b)(13) as such a citation makes it clear which cases the enhancement was intended to apply, which has the effect of decreasing litigation at sentencing. Further, POAG members preferred the two-level increase under USSG §2B1.1(b)(13), with a notation that a two-level increase under USSG §3B1.3 would ordinary apply, thereby limiting increase for these types of offenses to a total of four levels.

6. ACCEPTANCE OF RESPONSIBILITY

A defendant who enters a plea of guilty must admit to the elements of the offense; however, at the time of sentencing, the focus is on the concept of relevant conduct when determining if a defendant is eligible for an Acceptance of Responsibility reduction. The Commission is seeking comment on whether the references to relevant conduct should be removed from USSG §3E1.1 and, instead, focus only on the elements of the offense of conviction. POAG notes that relevant conduct is a broad concept that seeks to capture actual offense conduct versus the charged conduct, and that it can include conduct underlying charges that have been, or will be dismissed. As such, the current structure of USSG §3E1.1 requires defendants to "not falsely deny" any additional alleged conduct that is considered to be relevant conduct. POAG recommends that relevant conduct continue to serve as a basis for determining if a defendant is eligible for an Acceptance of Responsibility reduction out of concern that focusing on the elements of the offense would likely have the effect of increasing the amount of litigation at sentencing. Further, relying on relevant conduct in determining if a defendant is eligible for an Acceptance of Responsibility reduction is consistent with the rest of the guideline applications that are based upon relevant conduct. POAG believes that this approach has generally worked well and does not have any concerns regarding this part of the process.

The Commission is also seeking comment on whether USSG §3E1.1, comment. (n.1), should be amended by striking "However, a defendant who falsely denies, or frivolously contests, relevant conduct that the court determines to be true has acted in a manner inconsistent with acceptance of responsibility," and replacing it with "In addition, a defendant who makes a non-frivolous challenge to relevant conduct is not precluded from consideration for a reduction under subsection (a)." POAG supports this amendment, but recommends that references to "not falsely deny" or "non-frivolous" in USSG §3E1.1, comments. (n.1(A)) and (n.3), be replaced with "frivolously deny" so as to avoid the use of double negatives in the application instructions. Further, POAG supports this amendment as it seeks to distinguish defendants who have objections based upon reason and fact from defendants who have objections that have no good faith basis. POAG also recommends that the Commission consider defining what constitutes "frivolous," as the layperson's understanding of that term may differ from the common legal definition.

The Commission identified the above noted issue as a priority out of concern that the Commentary to USSG §3E1.1 encourages courts to deny an Acceptance of Responsibility reduction when a defendant pleads guilty and accepts responsibility for the offense of conviction, but unsuccessfully challenges the presentence report's assessment of relevant conduct or the application of a Specific Offense Characteristic. As it is currently written, the Commentary in USSG §3E1.1 requires a defendant to "not falsely deny any additional relevant conduct," which has been interpreted by some to mean that a reduction is not appropriate if the defendant falsely denies conduct that is determined to be relevant conduct. If that was not the Commission's intent, then POAG would support an amendment to the Commentary to USSG §3E1.1 to clarify that unsuccessful challenges to relevant conduct do not preclude a defendant from being eligible for an Acceptance of Responsibility reduction and that such amendment be significant enough that it creates a new standard under this guideline. POAG believes the aforementioned amendments to USSG §3E1.1 could increase due process for defendants who have legitimate challenges to relevant conduct and lessens their risk for automatic acceptance of responsibility denials in these cases.

Further, POAG recommends that USSG §3E1.1, comment. (n.5), which directs that "The sentencing judge is in a unique position to evaluate a defendant's acceptance of responsibility. For this reason, the determination of the sentencing judge is entitled to great deference on review," be stricken from the Guidelines Manual. POAG believes that the Guidelines Manual should focus on application instructions while leaving the issue of standard of review to the discretion of the appellate courts.

7. MISCELLANEOUS

In August 2016, the Commission indicated that one of its priorities would be the "[s]tudy of offenses involving MDMA/Ecstasy, synthetic cannabinoids (such as JWH-018 and AM-2201), and synthetic cathinones (such as Methylone, MDPV, and Mephedrone), and consideration of any amendments to the Guidelines Manual that may be appropriate in light of the information obtained from such study." See United States Sentencing Commission, "Notice of Final Priorities," 81 FR

58004 (Aug. 24, 2016). The Commission intends that this study will be conducted over a two-year period and will solicit input, several times during this period, from experts and other members of the public. The Commission further intends that in the amendment cycle ending May 1, 2018, it may, if appropriate, publish a proposed amendment as a result of the study.

POAG supports the continuation of this study. Officers noted this is a growing problem with an increase in synthetic cathinones and synthetic cannabinoids appearing in various districts. Currently there are approximately 256 synthetic cannabinoids listed as controlled substances and controlled substance analogues. POAG also discussed the ongoing problems with Methylone, Molly, Fentanyl, and bath salts.

When a drug trafficking offense involves a controlled substance not specifically referenced in the guidelines, the Commentary to USSG §2D1.1 instructs the court to "determine the base offense level using the marihuana equivalency of the most closely related controlled substance referenced in [§2D1.1]." USSG §2D1.1, comment. (n.6). The guidelines then provide a three-step process for making this determination. USSG §2D1.1, comment. (n.6, 8). In following this three-step process, POAG members indicated probation officers are doing extensive research and evaluation for the Presentence Report, and then the courts are holding similarly extensive hearings before ruling on the analysis. Further discussion revealed that, even after the analysis is made, there is inconsistency in the marijuana equivalencies that are used around the country. Some courts determine the synthetic smokeable cannabinoid substances are most closely related to Synthetic Tetrahydrocannabinol (THC), and others, marijuana. This is creating an inconsistency in guideline calculations utilizing various marijuana equivalency ratios; however, the majority of the POAG members indicated their officers were utilizing a 1:167 ratio with synthetic smokeable cannabinoids being most closely related to THC. There have been instances when courts have used a 1:167 ratio, that they found the result to be extremely excessive, and sentenced the defendant outside of the advisory guidelines.

Courts have also struggled with issues of notice, wherein the defendants were manufacturing, producing, and/or selling synthetic smokeable cannabinoids that were analogues of JWH-018 without public information or legal guidance available that could put the defendants on notice that AM-2201 and XLR-11 are analogues of JWH-018.

Courts have also struggled in determining the correct ratio for Methylene, and some have compared it to MDMA, while others have held hearings with expert witnesses in order to fashion what they believe to be a reasonable drug conversion rate. In some instances, courts have used a 1:500 ratio, while others have found that a 1:250 ratio or a 1:200 ratio is more appropriate.

In addition, POAG discussed the means by which the synthetic smokeable cannabinoids are made. Defendants frequently obtain a pure form of the chemical from companies that obtain the chemical from outside of the United States. The defendants use warehouses, garages, or storage units as locations for producing the final product of synthetic smokeable cannabinoids. The defendants utilize cement mixers to effectively coat inert plant material by putting the plant material and the

liquid based synthetic cannabinoids into the cement mixer. Defendants have also utilized sprayers to spray the synthetic cannabinoid suspended in a delivery liquid onto the inert plant material. After the plant material is coated, the defendants allow it to dry. The defendants collect the dried, coated plant material and grind it up. It is then packaged for sale. POAG discussed the inconsistency in guideline applications when determining the quantity of synthetic smokeable cannabinoids used to calculate the guidelines. For example, some courts are using the entire weight of the substance (the inert plant material as well as the synthetic substance applied to the inert plant material), while others are attempting to extract the actual or estimated weight of the inert organic material and only using the weight of the synthetic, controlled substance.

Another issue POAG members discussed was the varying charging options prosecutors are using with synthetic cases. For example, defendants with synthetic smokeable cannabinoid cases have been charged with offenses involving drug distribution with guidelines found in USSG §2D1.1; fraud with guidelines found in USSG §2B1.1; misbranding with guidelines found in USSG §2N2.1; and money laundering with guidelines found in USSG §2S1.1.

The Commission asked for additional comments regarding the defendants involved in such cases. POAG noted that, like most offenses, defendants vary tremendously. The defendants involved in these cases range from young people who work as cashiers at establishments that sell these items and other legal items, all the way to business owners who own one or multiple such stores. The cases involve people who accept the pure form of the synthetic substance and engage in the activities necessary to coat the inert plant material with the illicit compounds. Defendants include chemists who test and submit fraudulent laboratory reports on the contents of the products. Some are corporations that finance the operations.

Finally, the Commission asked for comments regarding the harms posed by these activities. POAG members noted the dangers of these synthetic substances. In many cases, defendants are obtaining a chemical substance from China or other foreign location. The substance may be accurately labeled, but many times, it is not. The substance is then sprayed on an organic plant-type material, packaged, and sold in stores. It is made easily accessible and highly attractive to individuals, who are frequently younger, looking to get high. Courts have accepted information from the American Association of Poison Control Centers that describes the effects of synthetic smokeable cannabinoid usage that can be life threatening and can include severe agitation and anxiety; fast racing heartbeat; nausea and vomiting; muscle spasms, seizures, and tremors; psychotic episodes; and suicidal or other harmful thoughts and/or actions. In court cases, the argument has been made that the synthetic smokeable cannabinoids are more serious because they involve a single, highly pure chemical that causes a variety of outcomes depending on the user. The substance is not tempered by other chemicals naturally present in marihuana.

POAG supported the idea of additional study of all synthetics and would like a methodology to deal with these designer drugs. Determining these equivalencies is difficult and time consuming. These cases sometimes require chemical analysis reports and in some instances, chemists and other

experts to resolve contested drug quantity issues at sentencing. This causes disparity between districts/judges, and therefore, sentences. Additionally, POAG supports the Commission's efforts to further investigate Fentanyl, Methylone, Ethylone and other illicit synthetic compounds. POAG members observed that the producers of illicit synthetic compounds are continuously changing the formulas of the compounds to achieve the same effects through different, not-yet-illegal, means, and POAG respectfully recommends the Commission consider the continuous evolution of these substances when fashioning a solution.

The POAG members will continue to forward cases of interest to the Commission as the members observe them.

8. MARIHUANA EQUIVALENCY

The proposed amendment makes technical changes to USSG §2D1.1 to replace the term "marihuana equivalency" with "converted drug weight." The term "marihuana equivalency" is used in cases that involve a controlled substance that is not specifically referenced in the Drug Quantity Table as well as cases with more than one controlled substance where it is necessary to convert each of the drugs to its marihuana equivalency. Although the Commission received comment expressing concern that the term "marihuana equivalency" is misleading and results in confusion for individuals not fully versed in the guidelines, the POAG unanimously agreed that they have never experienced similar confusion by counsel, the defendant, or the court. POAG suggests that the confusion may be a result of the presentation of the information in the Presentence Report and noted that the report should be clear as to the actual drug(s) and drug quantity(ies) for which the defendant is accountable with a notation thereafter of the marihuana equivalency. POAG also suggests that the Commission should include clarification of the term in its training sessions both nationally and district wide. Additionally, there is considerable case law in every circuit that references "marihuana equivalency" and changing this term could potentially lead to further litigation with regard to determining drug equivalencies. The change will make it much harder to compare sentencing recommendations between newer cases, using the new conversion process, and older cases. Moreover, POAG noted the potential confusion that could result from the use of the term "converted drug weight." The proposed guideline defines this term as a "nominal reference designation that is to be used as a conversion factor…" Nevertheless, upon inspection of the Drug Quantity Table and the Drug Conversion Table, it is clear this term is the same as marihuana. Therefore, to avoid further confusion, it is POAG's recommendation to make no changes to the term "marihuana equivalency."

In conclusion, POAG would like to sincerely thank the United States Sentencing Commission for the opportunity to provide feedback on the proposed amendments.

Respectfully,

Probation Officers Advisory Group

February 2017

March 10, 2017

Judge William H. Pryor, Jr., Chair
United States Sentencing Commission
One Columbus Circle, N.E., Suite 2-500
Washington, DC 20002-8002

RE: Request for Public Comment (BAC 2210-40) - Synthetic Drugs

Dear Judge Pryor:

The Drug Policy Alliance appreciates this opportunity to provide comments as the Commission undertakes a two-year study of MDMA (3,4-Methylenedioxy-Methamphetamine) and novel psychoactive substances (NPS), specifically MDPV (Methylenedioxypyrovalerone), Methylone (3,4-Methylenedioxy-N-Methylcathinone), Mephedrone (4-Methylmethcathinone (4-MMC)), JWH-018 (1-Pentyl-1-3-1-(1-Naphthoyl)Indole) and AM-2201 (1-(5-Fluoropenty1)-3-(1-Naphthoyl)Indole) with the intention of determining whether amendments to the Guidelines Manual may be appropriate for criminal offenses involving these substances.

The Drug Policy Alliance (DPA) works to increase the degree to which drug use is treated as a health issue and advances evidence based drug policy grounded in compassion and human rights. We accordingly oppose policies that predominantly rely on the criminal justice system to address drug use. DPA educates lawmakers at both the federal and state level about illicit drugs and effective policy responses that reduce harms both from drug use and drug prohibition.

In 2016, DPA co-hosted a summit in New York titled *New Strategies for New Psychoactive Substances*, which brought together more than 30 scholars, activists, service providers and people who use drugs to share what is currently known about NPS, identify areas for future NPS research, discuss strategies for intervening when NPS use becomes harmful and for new forms of NPS drug regulation, and explore how messaging and media about NPS can become more constructive.[1] Some of the findings from this convening are reflected in these comments.

People use NPS for a multitude of reasons, not least of which to cope with everyday struggles and experience pleasure. There are anecdotal reports that some people use synthetic cannabinoids and other NPS as a replacement therapy to manage withdrawal from heroin and other substances. Since NPS are generally not detectable by most conventional drug screening panels, many individuals also use NPS as a substitute for marijuana and other illicit substances that are prohibited as a condition of maintaining employment, court-ordered supervision or access to services.

People are known to use NPS to maintain employment, including individuals working in occupations where drug testing is routine such as law enforcement and military service. Drug testing is often a condition of receiving social services such as temporary housing and public assistance, which can incentivize people who rely on these services and have a substance use disorder to substitute NPS for illicit drugs or alcohol. The same holds true for individuals who are under court-ordered supervision and must submit to drug testing as a condition of probation or parole or are subjected to drug testing as a condition of remaining enrolled in substance abuse treatment.

NPS use has been documented among law enforcement and military ranks and in other professions, in both rural and urban communities and across socioeconomic groups. However, the media's portrayal of people who use NPS has skewed toward some of the most visible people in society and especially in urban centers. Individuals who are homeless or lack permanent housing and who often suffer from co-occurring substance use and mental health disorders are heavily profiled by the media. Sensationalist and dehumanizing media reports of "zombies" highlight extreme cases that have heavily influenced policymakers' efforts to criminalize these substances.

Prohibition is driving the rapid emergence of new NPS compounds that are exacerbating dangers to public health. Banning NPS compounds by placing them in Schedule I of the federal Controlled Substances Act has not stopped manufacturers from selling banned substances - such as those under review by the Commission - or creating new compounds that skirt existing laws. Criminalization only incentivizes manufacturers to invent new substances to replace what was banned. As this process repeats, chemical compounds are manipulated in ways that have never been studied for their health effects, potentially increasing – not mitigating - the dangers to public health.

Packages of NPS are sold under many different names and can contain a variety of chemical compounds sprayed on plant leaves with varying levels of potency. Because NPS are constantly changing, people cannot know which exact drugs they are taking, how the drugs will physically or emotionally affect them, or how they will interact with medications and other substances. Law enforcement may argue that the rapid evolution of these substances warrants harsher sentences and more aggressive prohibition. This, however, is exactly what incentivized the production and marketing of synthetic cannabinoids and synthetic cathinones as a legal alternative to illicit substances.

How the Commission may decide to set guidelines with respect to the NPS compounds currently under review will influence lawmakers at both the federal and state level who must make policy decisions about NPS. A decision to make sentencing guidelines for offenses involving the specified NPS

compounds excessively punitive could influence lawmakers to pursue more aggressive criminalization with serious consequences.

Since Congress last added NPS compounds to Schedule I in 2012, hundreds of new chemical compounds have been created and distributed for sale in the United States. The Drug Enforcement Administration has also added NPS compounds to Schedule I using both its emergency scheduling and rulemaking authority. Each compound added to Schedule I triggers the application of federal drug sentencing laws. Because there a lack of common understanding as to what constitutes an ordinary psychoactive dose for many of these NPS compounds, Congress has not specified quantity triggers, meaning people who struggle with addiction can face draconian sentences for miniscule amounts of any substance added to Schedule I.

Criminalization can also exacerbate health risks from using drugs, by pushing risky behavior underground and making it more difficult for health authorities to study impacts on public health and get help to people who need it the most. A Schedule I designation also erects regulatory and funding barriers to research that make it far more difficult for researchers to get support from their sponsoring institutions to investigate controlled substances.

Criminalizing people who use and sell drugs can also amplify the risk of fatal overdoses and diseases, increases stigma and marginalization, and drives people away from needed treatment, health and harm reduction services. For example, fear of arrest is the most common reason that witnesses do not immediately call 911 in the event of an overdose.[2] The stigmatization of people who use and sell drugs is pervasive in society and it creates major barriers to treatment, health care and other vital services.[3]

Moreover, the use of scarce government funds to enforce, prosecute, and incarcerate people who use NPS substances puts further strain on criminal justice resources. The criminalization of people who use drugs is also a major driver of mass arrests in the United States. Each year, U.S. law enforcement makes more than 1.5 million drug arrests – more arrests than for all violent crimes combined. The overwhelming majority – more than 80 percent – are for possession *only*.[4] Year after year, more than a million people are caught in the criminal system for nothing more than drug possession or use.[5]

Black people are far more likely to be arrested for drug possession and use, even though rates of reported drug use do not differ substantially among people of different races and ethnicities.[6] Disparate enforcement of drug possession laws and harsh sentencing requirements have produced profoundly unequal outcomes for people of color, who experience discrimination at every stage of the judicial system.

People who are incarcerated are held in environments where risks of contracting or transmitting HIV and hepatitis C are greatly elevated, with insufficient testing, prevention, treatment and other public health services.[7] Many jails and prisons in the U.S. do not provide medically supervised or medication-assisted withdrawal.[8] Even after a person completes a period of incarceration, a criminal conviction for drug possession can result in the temporary or permanent loss of child custody, voting rights, employment, business loans, licensing, student aid, public housing and other public assistance. These "collateral consequences" of drug convictions intensify the struggles individuals face on the road to recovery and rehabilitation.

The most effective way to reduce harms associated with NPS are harm reduction and treatment programs, which connect people to services – especially housing and employment. There are other potential approaches to regulating NPS use other than outright prohibition and criminalization. In July 2013, New Zealand's parliament enacted a historic law that created an FDA-like process for approving NPS if their relative safety can be demonstrated. While the outlines of the law are unique to New Zealand, it is one example of a different approach to a public health issue. We also believe that demand for synthetic cannabinoids and other NPS could decrease precipitously if people could get legal and regulated access to marijuana.

The Commission is weighing what the specified NPS compounds actually do and which existing scheduled drug is "the most closely related controlled substance" to these NPS compounds for the purposes of sentencing a person to a term of incarceration. Apart from anecdotal reports from law enforcement, emergency room physicians, and limited data from government surveys and exposure reports from poison control centers, little is actually known about NPS and much of the existing research on NPS does not reflect the experiences of people who use drugs or the on-the-ground reality of why and how people are using NPS and their effects. Little is known about the substances themselves, their effects, the epidemiology of their use, or interventions and policies to reduce their harms.

Similarly, little is known about the "potential for addiction and abuse, the pattern of abuse and harms associated with abuse" of NPS, including those compounds that are the focus of the Commission's two-year study. The actual risk profile of various NPS are not well known. There is insufficient data on prevalence and the effects of these substances on health to definitively understand the risks associated with use.

It is our view that the Commission's evaluations of the specified NPS compounds under its review should be informed by epidemiological research that surveys a broad population to better understand how widespread the use of NPS is as well as adverse effects from using these substances. Ethnographic research is also needed to understand the range of reasons why

people choose NPS over other substances, exactly how they are using them, and what factors impact choices to use or not use NPS. Decisions regarding the appropriate sentencing guidelines should be based on the best possible and most rigorous science.

We appreciate the difficulty of determining an appropriate response to NPS within the Commission's mandate to set sentencing guidelines for scheduled substances. However, we urge the Commission to seek and consult the best possible science before making determinations about how the specified NPS compounds may be addressed in the Sentencing Guidelines. We also urge the Commission to consider the impact that these determinations will have on policymakers who must respond to the rapidly evolving nature of NPS.

With respect to the Commission's review of current Sentencing Guidelines for MDMA, we concur with Rick Doblin, Ph.D., in prepared testimony on behalf of the Multidisciplinary Association of Psychedelic Studies (MAPS),[9] that the Commission's decision to increase the mandatory minimum sentences for MDMA-related offenses in 2001 was not guided by science. Rather, this decision was informed by the same kinds of anecdotal and sensationalized information that has guided most NPS policy decisions in the United States. We believe that the MDMA Sentencing Guideline is excessively punitive and inappropriate given both what is known scientifically about the drug as well as its known therapeutic value. We urge the Commission to adjust the MDMA Sentencing Guideline downward to reflect these findings.

Thank you for considering our views,

Grant Smith
Deputy Director, National Affairs
Office of National Affairs
Drug Policy Alliance
Suite 925
1620 I Street NW
Washington, D.C. 20006

[1] A full program of the *New Strategies for New Psychoactive Substances* event can be found here: http://www.drugpolicy.org/sites/default/files/documents/Psychoactive_NPS_Program.pdf, and videos of the sessions are here: https://www.youtube.com/playlist?list=PLf6y9tNpg8wMugyNNxppsE_GPxBzXHM69.

[2] See Peter J. Davidson et al., "Witnessing Heroin-Related Overdoses: The Experiences of Young Injectors in San Francisco," *Addiction* 97, no. 12 (2002); S. E. Lankenau et al., "Injection Drug Users Trained by Overdose Prevention Programs: Responses to Witnessed Overdoses," *J Community Health* 38, no. 1 (2013); M. Tracy et al., "Circumstances of Witnessed Drug Overdose in New York City: Implications for Intervention," *Drug Alcohol Depend* 79, no. 2 (2005); K. C. Ochoa et al., "Overdosing among Young Injection Drug Users in San Francisco," *Addict Behav* 26, no. 3 (2001); Robin A. Pollini et al., "Response to Overdose among Injection Drug Users," *American journal of preventive medicine* 31, no. 3 (2006).

[3] Samuel R. Friedman et al., "Drug Arrests and Injection Drug Deterrence," *American Journal of Public Health* 101, no. 2 (2011): 344-49; S. R. Friedman et al., "Relationships of Deterrence and Law Enforcement to Drug-Related Harms among Drug Injectors in Us Metropolitan Areas," *AIDS* 20, no. 1 (2006): 93-99; Corey S. Davis et al., "Effects of an Intensive Street-Level Police Intervention on Syringe Exchange Program Use in Philadelphia, Pa," *American Journal of Public Health* 95, no. 2 (2005): 233-36; D. Wolfe, M. P. Carrieri, and D. Shepard, "Treatment and Care for Injecting Drug Users with Hiv Infection: A Review of Barriers and Ways Forward," *Lancet* 376, no. 9738 (2010): 355-66; E. Wood et al., "A Review of Barriers and Facilitators of Hiv Treatment among Injection Drug Users," *AIDS* 22, no. 11 (2008): 1247-56.

[4] Federal Bureau of Investigation, "Crime in the United States, 2014," (Washington, DC: U.S. Department of Justice, 2015). The number of drug arrests first exceeded 1.5 million in 1996 – and it has almost never fallen below that point since.

[5] Sean Rosenmerkel, Matthew Durose, and Jr. Donald Farole, "Felony Sentences in State Courts, 2006-Statistical Tables," (Washington, D.C.: Bureau of Justice Statistics, 2009), Tables 1.1 & 1.2.

[6] *See, for example,* National Research Council, *The Growth of Incarceration in the United States: Exploring Causes and Consequences* (Washington, D.C.: The National Academies Press, 2014).

[7] Thomas Kerr, Will Small, and Evan Wood, "The Public Health and Social Impacts of Drug Market Enforcement: A Review of the Evidence," *International Journal of Drug Policy* 16, no. 4 (2005): 210-20; S. A. Strathdee et al., "Hiv and Risk Environment for Injecting Drug Users: The Past, Present, and Future," *Lancet* 376, no. 9737 (2010). 268-284; Alex Stevens, "Applying Harm Reduction Principles to the Policing of Retail Drug Markets," (International Drug Policy Consortium, 2013); B. M. Mathers et al., "Hiv Prevention, Treatment, and Care Services for People Who Inject Drugs: A Systematic Review of Global, Regional, and National Coverage," *Lancet* 375, no. 9719 (2010); Global Commission on Drug Policy, "The War on Drugs and Hiv/Aids: How the Criminalization of Drug Use Fuels the Global Pandemic.," (2012).

[8] Legal Action Center, "Confronting an Epidemic: The Case for Eliminating Barriers to Medication-Assisted Treatment of Heroin and Opioid Addiction," March 2015, https://lac.org/wp-content/uploads/2014/07/LAC-The-Case-for-Eliminating-Barriers-to-Medication-Assisted-Treatment.pdf (accessed September 22, 2016), p. 6; Amy Nunn et. al., "Improving Access to Opiate Addiction Treatment for Prisoners," Addiction, vol. 110 (7) (Jun. 2010), p. 1312; Shannon Gwin Mitchell et. al, "Incarceration and opioid withdrawal: The experiences of methadone patients and out-of-treatment heroin users," Journal of Psychoactive Drugs, vol. 41(2) (June 2009), p. 145–152.

[9] Rick Doblin, Ph.D., Testimony to US Sentencing Commission Re: MDMA, Multidisciplinary Association for Psychedelic Studies, March 15, 2017

November 22, 2016

Christine Leonard, Director
Office of Legislative and Public Affairs
United States Sentencing Commission
(202) 502-4500
pubaffairs@ussc.gov

Dear Ms Leonard,

With regard to the Sentencing Commission review of the Guidelines that pertain to Synthetic Cannabinoids, I respectively submit the attached documents documents which support consideration of reducing the current 1:167 ratio.

Attached are three documents that support our position, including the Sentencing Order USA vs Hossain, whereas 11th District Judge Middlebrooks sentenced Hossain at a 1:7 ratio as opposed to the Sentencing Guidelines ratio of 1:167, stating in part, "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."

Judge Middlebrooks goes on to say, "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... This sentence range is more reasonable than the sentence that the Government suggests I impose, based off the 1:167 ratio".

Ms Leonard , also attached are the University of Mississippi Government studies that Judge Middlebrooks references, as well as, the declaration of Dr Nicholas Cozzi, University of Wisconsin School of Medicine and Public Health.

Ms Leonard, no one knows where the 167:1 ratio comes from. Research and data support the more reasonable 1:7 ratio. Sentencing reform can rest on many levels. Not just Congress. The Sentencing Commission has undertaken this review and we strongly urge you to consider these facts.

Thank you for your's and the Committee's consideration. Please keep us informed as to the status of meetings and updates as they pertain toward these issues.

Sincerely,
Jim Barrow

December 1, 2016

Christine Leonard, Director
Office of Legislative and Public Affairs
United States Sentencing Commission
(202) 502-4500
pubaffairs@ussc.gov

Dear Ms Leonard,

As a supplement to my letter of November 22, 2016, a copy of which is attached, I would like to make an additional statement.

The Commission review of Number 9 of the Priorities mentions in part the synthetic cannabinoid compounds JWH-018 and AM-2201.

While my original letter proposes new guidelines for these substances I think I should be clear that what really needs to be reviewed is the guideline for THC. The Guideline for THC is where the 167:1 multiplier originates. The courts have determined that THC is the most closely related substance to JWH-018 and AM-2201. That is the reason why these substances are likewise given the guideline of 167:1.

Ms Leonard, since the courts have determined this relationship, we are not challenging the relationship of these substances to THC. But we do question the 167:1 multiplier assigned to THC. The University of Mississippi Government study concluded that the average percentage of THC in marijuana is greater than 14%,which supports the 1:7 ratio Judge Middlebrooks used in the Hossain sentencing, as well as the declaration of Dr Nicholas Cozzi, University of Wisconsin School of Medicine and Public Health.

I have attached my original letter plus these supporting documents for review.

Thank you again for your's and the Committee's consideration and please keep us informed as to the status of meetings and updates as they pertain toward these issues.

Sincerely,

Jim Barrow

February 2, 2017

Christine Leonard, Director
Office of Legislative and Public Affairs
United States Sentencing Commission
(202) 502-4500
pubaffairs@ussc.gov

Dear Ms Leonard,

I trust that your new year is off to a great start.

I appreciate you accepting the letters and supplements that I've submitted to you and the committee in consideration of a reassessment of the synthetic cannabinoid compounds sentencing guidelines.

I see that the Commission has committed to a two-year study. But what exactly are they studying? The effects of the compounds like AM-2201? Several experts on both sides have testified to this already. Are they studying the fairness of disparity in sentences? This information is readily available. Notwithstanding the numerous cases around the country where the sentencing guidelines have ranged from 1:1, 1:7 and upwards to the 1:167, take for instance USA vs Reece. Here Reece, the number one defendant, was sentenced to 6 months home confinement because he was able to get his sentencing moved to his home state of Florida. The sentencing judge completely through out the 1:167. Meanwhile, his co-defendants in Louisiana were sentenced at 1:167 from 4-10 years incarceration.

While I appreciate that the commission has committed to a two-year study I urge the Commission to look at this from another point that would save the commission, the taxpayers and the defendants involved considerable time and resources.

With respect to Synthetic Cannabinoids, the Commission and the Courts were asked to determine the “most closely related substance”. In doing so, the Commission found that THC was the most closely related. Some Courts have agreed while many others have not because of the very high 1:167 multiplier. Chemically speaking THC may be the most closely related drug in the Guidelines. The problem with that is the THC multiplier that ends up being assigned these other compounds that many judges do not agree.

Attached are three documents that support our position, including the Sentencing Order USA vs Hossain, whereas 11th District Judge Middlebrooks sentenced Hossain at a 1:7 ratio as opposed to the Sentencing Guidelines ratio of 1:167, stating in part, "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."

Judge Middlebrooks goes on to say, "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... This sentence range is more reasonable than the sentence that the Government suggests I impose, based off the 1:167 ratio".

Ms Leonard , also attached are the University of Mississippi Government studies, funded by the National Institute on Drug Abuse, that Judge Middlebrooks references, as well as, the declaration of Dr Nicholas Cozzi, University of Wisconsin School of Medicine and Public Health.

Maybe the immediate issue before the Commission is not further studies on synthetic cannabinoids but to reassess the THC guideline. There is no further research or government or taxpayers resources required for this. The study has been done. The attached University of Mississippi study was funded by our government.

The current sentencing guidelines for the compounds marijuana and THC state:

SCHEDULE I MARIHUANA CONVERTED DRUG WEIGHT
1 gm of Marihuana/Cannabis, granulated, powdered, etc. = 1 gm of marihuana
1 gm of Tetrahydrocannabinol, Organic = 167 gm of marihuana
1 gm of Tetrahydrocannabinol, Synthetic = 167 gm of marihuana

If we know from the University of Mississippi government funded study that the current average potency in marijuana is 14% THC, how can the 1:167 ratio for THC stand?

Ms Leonard, no one knows where the 1:167 ratio comes from. Research and data support the more reasonable 1:7 ratio. Sentencing reform can rest on many levels. Not just Congress. The Sentencing Commission has undertaken this review and we strongly urge you to consider these facts.

Thank you for your's and the Committee's consideration. Please keep us informed as to the status of meetings and updates as they pertain toward these issues.

Sincerely,

Jim Barrow

U.S. v. HOSSAIN

Case No. 15-cr-14034-MIDDLEBROOKS.

UNITED STATES, Plaintiff, v. SAIFUL HOSSAIN, AHMED YEHIA KHALIFA, and AHMED MAHER ELHELW, Defendant.

United States District Court, S.D. Florida.

January 5, 2016.

Attorney(s) appearing for the Case

Saiful Hossain, Defendant, represented by Richard G. Lubin, Richard G. Lubin, PA & Fritz Joseph Scheller, Fritz Scheller, P.L..

Ahmed Yehia Khalifa, Defendant, represented by Mark Jon O'Brien.

Ahmed Maher Elhelw, Defendant, represented by Marc Shiner, Perlet & Shiner PA.

USA, Plaintiff, represented by Carmen M. Lineberger, U.S. Attorney's Office & Antonia J. Barnes, United States Attorney's Office.

SENTENCING ORDER

DONALD M. MIDDLEBROOKS, *District Judge*.

Defendant Saiful Hossain pleaded guilty to Counts I and II of the Superseding Indictment. Count I charges Hossain with conspiracy to import a controlled substance— XLR-11—in violation of 21 U.S.C. §§ 952(a) and 963. Count II charges him with conspiracy to manufacture, possess with intent to manufacture and

distribute a controlled substance—XLR-11—in violation of 21 U.S.C. §§ 841(a)(1) and 846. (DE 84).

XLR-11, a temporarily controlled substance, is not referenced in the Drug Quantity Table or Drug Equivalency Table of Section 2D 1.1 of the United States Sentencing Guidelines ("Guidelines"). 18 U.S.C. § 2D1.1. I held a hearing on December 11, 2015 to hear evidence on how XLR-11 should be considered at sentencing. On January 5, 2016, I heard argument on the role of Hossain in the instant offense, as well as § 3553 factors.

I. Background

XLR-11 is a "synthetic cannabinoid." [1] Synthetic cannabinoids act on two receptors in the human body, CB1 and CB2, to cause a "high" similar to what users experience while consuming marijuana. XLR-11, like other synthetic cannabinoids, typically comes to the United States from China as a powder, which is then applied to plant materials to be smoked, or liquidated to be used in vaporizers. (DE 229, Tr. at 65). Synthetic cannabinoids laced on plant materials are often marked as "herbal incense" products and can be purchased online or at gas stations.

Reports of XLR-11 use in the United States began in the first half of 2012. Because XLR-11 appeared only three years ago in the United States, knowledge about XLR-11 is limited. (DE 217-4, *Acute Kidney Injury Associated with Synthetic Cannabinoid Use).* Information about the effects of XLR-11 is further limited because in the synthetic drug market it is common for the drugs to be replaced by new, unregulated chemicals once one synthetic has been regulated. By one account, products are available for only about twelve to twenty four months before they are replaced by the next, unregulated wave. (DE 217-8, *Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs).*

JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, September 2010, Vol. 55, No. 5
doi: 10.1111/j.1556-4029.2010.01441.x
Available online at: interscience.wiley.com

PAPER

CRIMINALISTICS

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Potency Trends of Δ^9-THC and Other Cannabinoids in Confiscated Cannabis Preparations from 1993 to 2008*

ABSTRACT: The University of Mississippi has a contract with the National Institute on Drug Abuse (NIDA) to carry out a variety of research activities dealing with cannabis, including the Potency Monitoring (PM) program, which provides analytical potency data on cannabis preparations confiscated in the United States. This report provides data on 46,211 samples seized and analyzed by gas chromatography-flame ionization detection (GC-FID) during 1993–2008. The data showed an upward trend in the mean Δ^9-tetrahydrocannabinol (Δ^9-THC) content of all confiscated cannabis preparations, which increased from 3.4% in 1993 to 8.8% in 2008. Hashish potencies did not increase consistently during this period; however, the mean yearly potency varied from 2.5–9.2% (1993–2003) to 12.0–29.3% (2004–2008). Hash oil potencies also varied considerably during this period (16.8 ± 16.3%). The increase in cannabis preparation potency is mainly due to the increase in the potency of nondomestic versus domestic samples.

KEYWORDS: cannabichromene (CBC), cannabidiol (CBD), cannabigerol (CBG), cannabinoids, cannabinol (CBN), cannabis, criminalistics, forensic science, gas chromatography-flame ionization detection (GC-FID), marijuana, potency, tetrahydrocannabivarin (THCV), Δ^9-tetrahydrocannabinol (Δ^9-THC)

Marijuana, the crude drug derived from *Cannabis sativa* L. pistillate inflorescence, is the most widely cultivated and consumed illicit drug in the world despite being under international control for eight decades (1,2). The reason for this is mainly attributed to two factors; namely, relaxation of cannabis law enforcement relative to other illicit drugs and the enormous extent of cannabis production and consumption. Furthermore, cannabis is cultivated both indoors and outdoors, often on a small scale, facilitating inconspicuous trading. Hashish (hash) and hash oil are two preparations designed to minimize the volume of the drug, thereby minimizing confiscation.

The Δ^9-tetrahydrocannabinol (Δ^9-THC) potency (concentration or content) of cannabis depends on soil and climate conditions, variety (phenotype), and cultivation techniques, with different parts of the plant having varying concentrations of the drug (3–6). The total number of identified cannabis constituents has increased from 489 in 2005 (7) to 537 in 2009, while the number of cannabinoids has increased from 70 to 109 (8–13). The main psychoactive ingredient in cannabis is Δ^9-THC (14,15); however, other cannabinoids have also demonstrated pharmacological activities, e.g., the nonpsychotropic cannabinoid cannabidiol (CBD) displays antipsychotic, antihyperalgesic, anticonvulsant, neuroprotective, and antiemetic properties (16–18).

The complex political, medical, cultural, and socioeconomic issues associated with cannabis necessitates not only public and governmental scrutiny, but especially scientific inquiry (1,2,19–24). The National Institute on Drug Abuse (NIDA) Potency Monitoring (PM) program at the National Center for Natural Products Research, University of Mississippi, provides analytical potency data on cannabis preparations seized in the United States, including both domestic and nondomestic material (25–28). A survey of the literature reporting similar programs in other countries revealed a number of comprehensive studies, e.g., England (2004–2005) (29), Brazil (2006–2007) (30), Netherlands (1999–2007) (31–34), Italy (1997–2004) (35), New Zealand (1976–1996) (36), and Australia (37), as well as a number of general reviews pertaining to cannabis potency trends (1,2,21,22,32,38,39).

This report covers 46,211 cannabis preparations confiscated and analyzed by gas chromatography-flame ionization detection (GC-FID) in the United States during 1993–2008, following on previous reports covering 1972–1997 (36,297 samples) (25–28). The total number of samples received during this period (1993–2008) was 47,583 as of 30 March 2009. The number of samples analyzed was 46,211, with 1,372 samples not analyzed for a variety of reasons, including insufficient material, wet material, and material containing only seeds and stems. Statistical analysis on the mean yearly Δ^9-THC concentration is included to establish the potency trend over time. Data on hashish, hash oil, and the potencies of

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*This project was supported by the National Institute on Drug Abuse (contract number N01DA-5-7746).

Received 15 May 2009; and in revised form 14 July 2009; accepted 31 July 2009.

cannabichromene (CBC), cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV) are also presented.

Materials and Methods

Sample Acquisition

All samples analyzed in this investigation were confiscated during 1993 through 2008 by United States Federal and State law enforcement agencies.

Sample Identification

Sample classification is based on physical characteristics according to the following guidelines:

Cannabis Samples—All samples were received as raw plant material. These samples were further categorized as follows:

- *Marijuana* (known as herbal cannabis in Europe): usually found in four forms: (i) loose material - loose cannabis plant material with leaves, stems, and seeds; (ii) leaves - cannabis plant material consisting primarily of leaves; (iii) kilo bricks - compressed cannabis with leaves, stems, and seeds (typical Mexican packaging); and (iv) buds - flowering tops of female plants with seeds.
- *Sinsemilla*: flowering tops of unfertilized female plants with no seeds (subdivided as for marijuana with most samples being classified as buds).
- *Thai sticks*: leafy material tied around a small stem (typical Thailand packaging).
- *Ditchweed*: fiber type wild cannabis found in the Midwestern region of the United States (subdivided as for marijuana).

Hashish Samples—Hashish (known as cannabis resin in Europe) is composed of the resinous parts of the flowering tops of cannabis, mixed with some plant particles and shaped into a variety of forms, e.g., balls, sticks, or slabs. It is generally very hard with a dark green or brownish color.

Hash Oil Samples—Hash oil is a liquid or semi-solid concentrated extract of cannabis plant material. Depending on the process used to prepare hash oil, it is usually dark green, amber, or brownish.

Sample Storage

All samples are stored in a vault at controlled room temperature (17 ± 4°C).

Domestically Cultivated Cannabis

Cannabis preparations that have been verified as being produced from plants grown in the United States are classified as domestic samples, whereas all other samples are classified as nondomestic.

Sample Preparation

Cannabis—The samples were manicured in a 14 mesh metal sieve to remove seeds and stems. Duplicate samples (2 × 0.1 g) were extracted with internal standard solution (ISTD) [3 mL, 4–androstene-3,17-dione (100 mg) (Sigma Aldrich, St. Louis, MO) in chloroform/methanol (100 mL, 1:9, v/v), 1 mg/mL] at room temperature for 1 h. The extracts were transferred to GC vials via filtration through sterile cotton plugs, followed by capping of the vials (25).

Hashish—Samples were powdered using a mortar and pestle or an electric blender. Duplicate samples (2 × 0.1 g) were extracted following the procedure outlined for cannabis samples (*vide supra*).

Hash Oil—Duplicate samples (2 × 0.1 g) were extracted with ISTD [4 mL, 4-androstene-3,17-dione (50 mg) in absolute ethanol (50 mL), 1 mg/mL] as follows: maceration at room temperature for 2–4 h, sonication for 5 min, addition of absolute ethanol (20 mL), and sonication for 5 min. The extracts were transferred to GC vials as described earlier.

Chromatographic Analysis

GC analyses were performed using Varian CP-3380 gas chromatographs, equipped with Varian CP-8400 automatic liquid samplers, capillary injectors, dual flame ionization detectors, and DB-1MS columns (15 m × 0.25 mm × 0.25 μm) (J&W Scientific, Folsom, CA). Data were recorded using a Dell Optiplex GX1 computer and Varian Star workstation software (version 6.1). Helium was used as carrier and detector makeup gas with an upstream indicating moisture trap and a downstream indicating oxygen trap. Hydrogen and compressed air were used as the combustion gases. The following instrument parameters were employed: air, 30 psi (300 mL/min); hydrogen, 30 psi (30 mL/min); column head pressure, 14 psi (1.0 mL/min); split flow rate, 100 mL/min; split ratio, 50:1; septum purge flow rate: 5 mL/min; makeup gas pressure, 20 psi (30 mL/min); injector temperature, 240°C; detector temperature, 270°C; oven program, 170°C (hold 1 min) to 250°C at 10°C/min (hold 3 min); run time, 12 min; injection volume, 1 μL. The instruments are daily maintained and calibrated to ensure a Δ^9-THC/internal standard response factor ratio of one.

Calculation of Concentrations

The concentration of a specific cannabinoid is calculated as follows:

$$cannabinoid\% = \frac{GC[area](cannabinoid)}{GC[area](ISTD)} \times \frac{amount(ISTD)}{amount(sample)} \times 100$$

Statistical Analysis

The mean and standard deviation (SD) of the sample concentrations were calculated for the combined data set, by year and sample type, and for domestic and nondomestic samples. Normal and outlier cannabis samples were determined based on the mean and SD of the Δ^9-THC concentration for each year and sample type (40). Normal samples are defined as samples with potencies in the range: mean ± 2.5 × SD. Outlier samples are defined as samples with potencies that fall outside this range. The precision of the mean was determined through 95% confidence intervals (CIs). The CI was calculated using the Excel function TINV(probability, degrees of freedom), which returns the inverse or t-value of the Student's t-distribution as a function of the probability associated with the two-tailed Student's t-distribution and the degrees of freedom [number of samples (n) – 1]. The CI range is subsequently calculated as the mean ± the product of the TINV value and the standard error of the mean (SEM), i.e., the SD divided by the square root of the number of samples, thus mean ± SEM × TINV

[$SEM = SD/\sqrt{n}$, TINV = TINV(0.05, $n - 1$)]. A 95% CI is a range of values that contains the true mean of the population with 95% certainty. The Pearson product-moment correlation coefficient (r) was calculated using the Excel PEARSON function, and the standard error for the predicted mean values for each year in the regression was calculated using the Excel STEYX function.

Results and Discussion

During the past 16 years (1993–2008), 46,211 samples of cannabis preparations confiscated in the United States, representing *c.* 8,321 tons, were analyzed at the University of Mississippi PM laboratory (Table 1). The PM program has analyzed 67,227 samples to date since 1968 (25–28). Samples classification is performed by the submitting agency and verified by the PM laboratory. Prior to 1995, there was no classification in the database for ditchweed; therefore, all ditchweed samples were classified as marijuana. However, interest in monitoring ditchweed samples and its effect on the overall potency of confiscated marijuana necessitated this category on the sample report form since 1995. The data presented in this report on ditchweed samples prior to 1995 were generated by retrospective review of the PM data. Marijuana samples with Δ^9-THC <1% and CBD > Δ^9-THC were classified as ditchweed. Cannabis, i.e., marijuana, sinsemilla, Thai sticks, and ditchweed, represents the overwhelming majority of the samples confiscated in the United States (98.7%), while the hashish and hash oil combined contribution is <1.5% (Table 1). Marijuana typically represents at least 50% of the samples. Sinsemilla samples gradually increased from 2002, with a concurrent decrease in the number of marijuana samples.

The yearly arithmetic mean Δ^9-THC concentration for the different types of cannabis samples shows large variation within categories and over time, with only the ditchweed samples being relatively constant (Table 2). Hashish and hash oil sample potencies

TABLE 1—*Number of samples (*n*) analyzed by type and year.*

	All	Marijuana*		Sinsemilla*		Thai sticks*		Ditchweed*		Hashish†		Hash oil†	
Year	*n*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
1993	3412	3033	88.9	123	3.6	0	0.0	200	5.9	39	1.1	17	0.5
1994	3327	3032	91.1	104	3.1	0	0.0	148	4.4	29	0.9	14	0.4
1995	4791	4430	92.5	164	3.4	2	0.04	163	3.4	19	0.4	13	0.3
1996	2455	2148	87.5	169	6.9	0	0.0	118	4.8	12	0.5	8	0.3
1997	2495	2273	91.1	121	4.8	0	0.0	60	2.4	31	1.2	10	0.4
1998	2283	2075	90.9	101	4.4	0	0.0	87	3.8	15	0.7	5	0.2
1999	2692	2450	91.0	136	5.1	0	0.0	72	2.7	23	0.9	11	0.4
2000	3148	2928	93.0	113	3.6	0	0.0	73	2.3	27	0.9	7	0.2
2001	2716	2398	88.3	235	8.7	0	0.0	63	2.3	13	0.5	7	0.3
2002	2413	1789	74.1	528	21.9	0	0.0	75	3.1	16	0.7	5	0.2
2003	2517	1893	75.2	538	21.4	0	0.0	66	2.6	16	0.6	4	0.2
2004	2637	1815	68.8	731	27.7	0	0.0	62	2.4	25	0.9	4	0.2
2005	3004	1964	65.4	931	31.0	0	0.0	56	1.9	47	1.6	6	0.2
2006	2890	1770	61.2	1032	35.7	0	0.0	53	1.8	32	1.1	3	0.1
2007	3097	1635	52.8	1327	42.8	0	0.0	47	1.5	70	2.3	18	0.6
2008	2334	1151	49.3	1093	46.8	0	0.0	28	1.2	50	2.1	12	0.5
1993–2008	46,211	36,784	79.6	7446	16.1	2	0.0	1371	3.0	464	1.0	144	0.3

*Total cannabis: 45,603 samples (98.7%).
†Total hashish + hash oil: 608 samples (1.3%).

TABLE 2—*Mean and SD Δ^9-THC concentration by type of sample and year.*

	All		Marijuana		Sinsemilla		Thai sticks		Ditchweed		Hashish		Hash oil	
Year	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1993	3.4	2.9	3.4	2.4	5.8	3.8	0.0	0.0	0.4	0.3	6.6	6.7	16.5	11.7
1994	3.5	2.5	3.5	2.1	7.5	4.8	0.0	0.0	0.4	0.3	4.6	3.6	11.6	7.9
1995	3.8	2.3	3.7	1.8	7.5	4.4	4.5	0.8	0.4	0.4	3.6	3.7	13.2	8.9
1996	4.1	3.0	3.9	2.2	9.2	4.7	0.0	0.0	0.4	0.3	2.5	1.4	12.8	9.5
1997	4.6	3.7	4.3	2.7	11.6	5.9	0.0	0.0	0.5	0.3	8.9	9.3	18.2	9.0
1998	4.5	3.6	4.2	2.9	12.3	5.2	0.0	0.0	0.4	0.3	5.9	5.2	15.8	9.9
1999	4.6	4.0	4.2	3.2	13.4	4.7	0.0	0.0	0.4	0.3	4.9	4.2	16.2	10.7
2000	4.9	4.0	4.7	3.4	12.8	4.4	0.0	0.0	0.4	0.3	4.2	4.2	28.6	11.6
2001	5.4	4.1	5.0	3.5	9.6	5.4	0.0	0.0	0.4	0.3	8.5	5.9	19.4	8.1
2002	6.4	5.1	5.1	3.4	11.4	5.7	0.0	0.0	0.4	0.3	9.1	8.5	22.5	28.3
2003	6.3	4.8	5.0	3.1	11.6	5.7	0.0	0.0	0.3	0.3	9.2	7.6	15.5	6.9
2004	7.2	5.8	5.4	3.6	11.9	6.0	0.0	0.0	0.4	0.3	18.9	15.1	31.3	34.6
2005	7.2	5.3	5.2	3.2	11.6	5.7	0.0	0.0	0.4	0.3	12.0	10.3	6.4	2.8
2006	7.8	6.5	5.6	4.0	11.2	6.5	0.0	0.0	0.3	0.2	29.3	19.7	18.7	26.1
2007	8.8	7.4	6.1	3.7	11.1	6.6	0.0	0.0	0.4	0.3	27.7	18.4	24.9	29.6
2008	8.8	6.9	5.8	3.9	11.5	6.2	0.0	0.0	0.4	0.3	23.1	19.6	6.5	9.7
1993–2008	5.6	5.0	4.5	3.1	11.1	6.1	4.5	0.8	0.4	0.3	14.1	15.7	16.8	16.3
95% CI range*	5.53–5.62		4.46–4.53		11.01–11.28		0.00–11.69		0.37–0.40		12.69–15.56		14.07–19.45	

SD, Standard deviation.
*95% CI range: range of values that contains the true mean with 95% certainty.

showed the most variability over the 16-year period. The mean and SD for these categories were 14.1% ± 15.7% and 16.8% ± 16.3%, respectively. The marijuana Δ^9-THC concentration appeared to gradually increase from 1993 to 2008, with a Pearson product-moment correlation coefficient (r) of 0.982 and a standard error for the predicted mean values of 0.17 (Fig. 1). The mean Δ^9-THC concentration for sinsemilla fluctuated considerably, ranging from a minimum in 1993 (5.8% ± 3.8%) to a maximum in 1999 (13.4% ± 4.7%) (Table 2, Fig. 1). Other than the expected finding that the yearly mean potencies of sinsemilla samples were much higher than that for marijuana samples, there did not appear to be any meaningful trend in the mean potency of the sinsemilla samples. The mean Δ^9-THC concentration of sinsemilla samples between 1993 and 2000 increased from 5.8% to 12.8% (121.8% increase), dropping slightly in 2001 (9.6%), and stabilizing between 2002 and 2008 (11.5% ± 0.3%) (Fig. 1).

The change in cannabis potency over the past 40 years has been the subject of much debate and controversy. This report investigates the influence of outlier samples on the overall mean concentration of Δ^9-THC for the time period studied in an attempt to clarify this issue. Normal and outlier cannabis preparations are samples with Δ^9-THC concentrations that fall within and outside the range mean ± 2.5 × SD, respectively.

The outlier samples for marijuana and sinsemilla represent 2.4% and 0.5%, respectively, of the total samples for each type (Table 3). The distribution of Δ^9-THC concentrations is positively skewed,

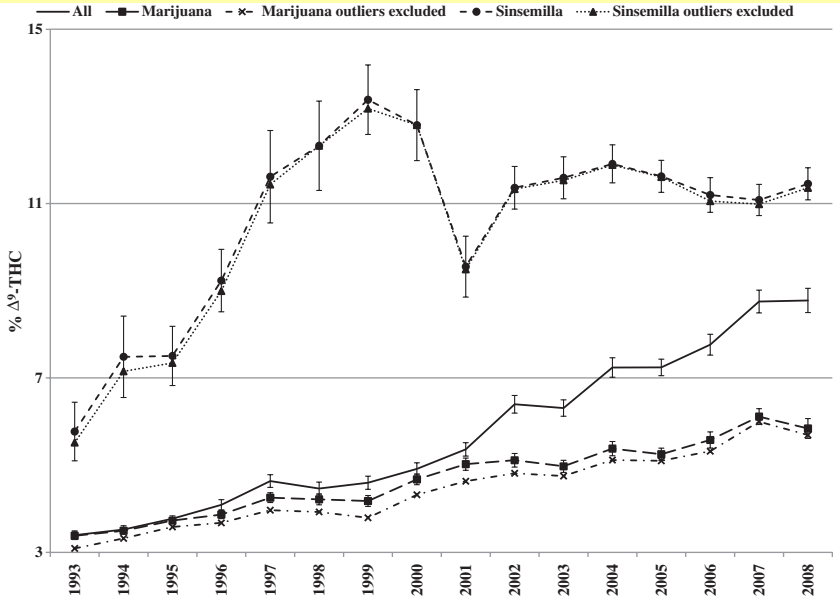

FIG. 1—*Mean Δ^9-THC concentration with 95% confidence intervals for all samples, marijuana and sinsemilla samples, and marijuana and sinsemilla samples with outliers excluded.*

TABLE 3—*Mean and SD Δ^9-THC concentration for marijuana and sinsemilla samples with outliers* excluded.*

	Marijuana					Sinsemilla				
	Outliers	All samples		Outliers excluded		Outliers	All samples		Outliers excluded	
Year	%	Mean	SD	Mean	SD	%	Mean	SD	Mean	SD
1993	2.9	3.4	2.4	3.1	1.7	2.4	5.8	3.8	5.5	3.4
1994	2.3	3.5	2.1	3.3	1.7	1.9	7.5	4.8	7.2	4.2
1995	2.0	3.7	1.8	3.6	1.5	1.2	7.5	4.4	7.3	4.2
1996	2.3	3.9	2.2	3.7	1.8	1.8	9.2	4.7	9.0	4.4
1997	3.1	4.3	2.7	4.0	2.2	0.8	11.6	5.9	11.4	5.6
1998	2.7	4.2	2.9	3.9	2.3	0.0	12.3	5.2	12.3	5.2
1999	3.5	4.2	3.2	3.8	2.4	1.5	13.4	4.7	13.2	4.4
2000	3.2	4.7	3.4	4.3	2.8	0.0	12.8	4.4	12.8	4.4
2001	3.4	5.0	3.5	4.6	2.8	0.4	9.6	5.4	9.5	5.4
2002	2.5	5.1	3.4	4.8	2.8	0.2	11.4	5.7	11.3	5.7
2003	2.1	5.0	3.1	4.8	2.7	0.4	11.6	5.7	11.5	5.6
2004	2.1	5.4	3.6	5.1	3.1	0.1	11.9	6.0	11.9	6.0
2005	1.5	5.2	3.2	5.1	3.0	0.1	11.6	5.7	11.6	5.7
2006	2.0	5.6	4.0	5.3	3.5	0.8	11.2	6.5	11.1	6.3
2007	0.9	6.1	3.7	6.0	3.5	0.5	11.1	6.6	11.0	6.5
2008	1.1	5.8	3.9	5.7	3.7	0.5	11.5	6.2	11.4	6.1
1993–2008	2.4	4.5	3.1	4.2	2.7	0.5	11.1	6.1	11.1	6.0
95% CI range†	–	4.46–4.53		4.22–4.27		–	11.01–11.28		10.92–11.20	

SD, Standard deviation.
*Mean – 2.5 × SD > Outlier > Mean + 2.5 × SD.
†95% CI range: range of values that contains the true mean with 95% certainty.

i.e., all outliers are samples with potencies higher than the mean potency. It is therefore important that the potential effect of the outliers is examined to determine whether the apparent trend of increasing potency is real or simply a statistical artifact. A comparison of the mean potency of marijuana and sinsemilla samples calculated for all samples versus for samples with outliers excluded indicates that the mean Δ^9-THC concentration decreases for each year when the outliers are excluded (Table 3, Fig. 1). However, the general pattern of increasing potency of marijuana samples since 1993 appears to exist even when outliers are excluded. The Pearson product-moment correlation coefficient (*r*) and standard error for the predicted mean values after exclusion of marijuana sample outliers were 0.981 and 0.18, respectively. Because of the greater variability found in the potency of sinsemilla samples, fewer cases were excluded as outliers and thus there was little effect on the mean potency for each of the years reported (Table 3, Fig. 1). The mean Δ^9-THC concentration for marijuana and sinsemilla samples decreased by 0.24% and 0.08%, respectively, after exclusion of the outliers.

Further evidence that the mean Δ^9-THC concentration for marijuana may be increasing is inferred by the analysis of the percentage of samples each year with Δ^9-THC concentration more than 3%, 5%, and 9%. Marijuana samples with Δ^9-THC >9% increased from 3.23% (1993) to a maximum 21.47% (2007). Conversely, the number of marijuana sample containing Δ^9-THC <3% decreased between 1993 and 2007, with a slight increase in 2008 (Fig. 2). The trend for sinsemilla samples with Δ^9-THC >9% followed a similar pattern to the overall trend for the yearly mean potencies

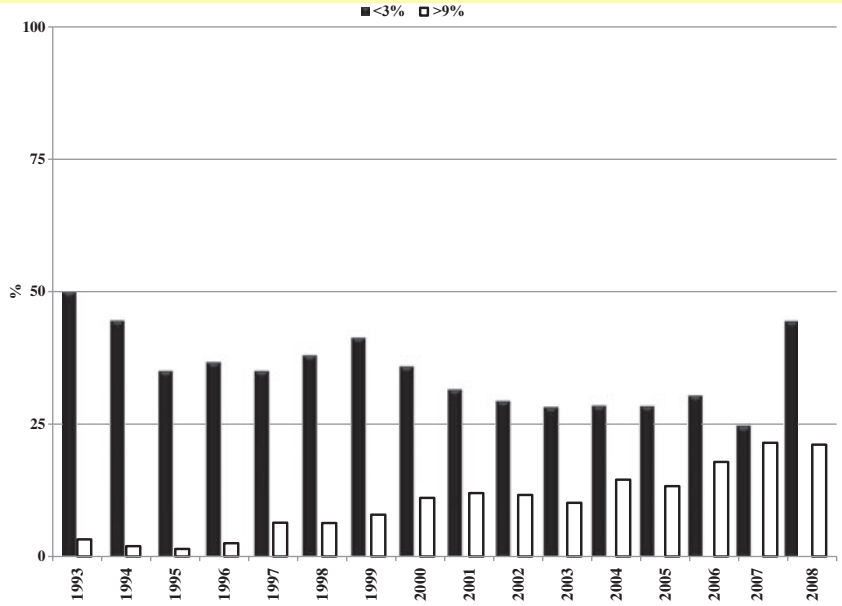

FIG. 2—*Prevalence of low (<3%) and high (>9%) potency marijuana samples.*

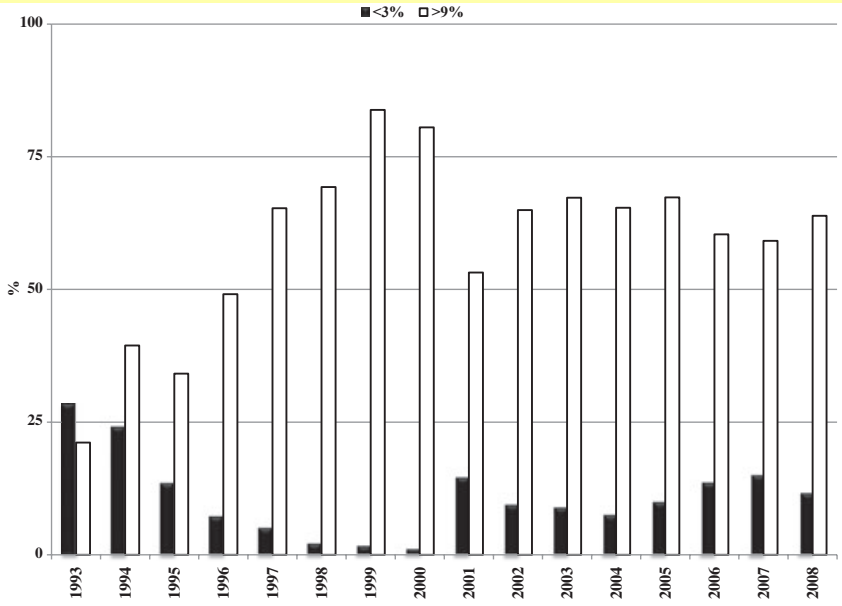

FIG. 3—*Prevalence of low (<3%) and high (>9%) potency sinsemilla samples.*

(Figs 1 and 3). Considering the large number of cannabis samples analyzed each year, it is doubtful that these observations are statistical artifacts.

The overall number of samples, mean, SD, maximum and minimum concentrations of Δ^9-THC for the different types of samples categorized by origin, i.e., domestic or nondomestic, indicates that ditchweed is mainly a domestic product, whereas Thai sticks, hashish, and hash oil are nondomestic products (Table 4). Marijuana and sinsemilla samples represent more than 95% of all seizures. It is important to mention that samples are classified as being of domestic origin only if the seizure is made from a growing operation (indoor or outdoor) within the United States. All other samples are classified as being nondomestic, although they could possibly have been produced in the United States prior to seizure. It is also important to note that all nondomestic sample seizures made by the DEA are of final products produced from mature plant material. In contrast, the domestic samples provided by the state eradication programs are seized at different stages of plant maturity. Overall, the number of samples of known domestic origin represents approximately one-third of all samples confiscated. The number of nondomestic seizures was consistently higher when compared to that of domestic seizures (Fig. 4). The mean Δ^9-THC concentration for nondomestic cannabis samples showed a gradual increase, while domestic samples had little fluctuation (Fig. 5).

The mean concentration of the minor cannabinoids CBC, CBD, CBN, CBG, and THCV were also monitored (Table 5). CBD is the major cannabinoid found in ditchweed and is present in elevated amounts in intermediate type cannabis (moderate levels of both Δ^9-THC and CBD) used to make hashish. The cannabinoid content of hashish and hash oil samples shows that, while hashish

TABLE 4—*Number of samples (*n*), mean, SD, maximum and minimum Δ^9-THC concentration by origin and type of sample.*

Origin	Type	*n*	Mean	SD	Maximum	Minimum
Domestic	Marijuana	10,308	3.0	2.8	24.7	<0.01
	Sinsemilla	3067	7.9	5.5	33.1	0.1
	Thai sticks	0	–	–	–	–
	Ditchweed	1257	0.4	0.3	2.4	<0.01
	Hashish	3	34.0	25.4	52.9	5.1
	Hash oil	2	0.2	0.01	0.23	0.21
	1993–2008	14,637	3.8	4.1	52.9	<0.01
Nondomestic	Marijuana	26,476	5.1	3.0	37.2	<0.01
	Sinsemilla	4379	13.4	5.4	32.3	0.5
	Thai sticks	2	4.5	0.8	5.1	4.0
	Ditchweed	114	0.4	0.3	1.2	0.1
	Hashish	461	14.0	15.6	66.3	<0.01
	Hash oil	142	17.0	16.3	81.7	<0.01
	1993–2008	31,574	6.4	5.1	81.7	<0.01
All Samples	Marijuana	36,784	4.5	3.1	37.2	<0.01
	Sinsemilla	7446	11.1	6.1	33.1	0.1
	Thai sticks	2	4.5	0.8	5.1	4.0
	Ditchweed	1371	0.4	0.3	2.4	<0.01
	Hashish	464	14.1	15.7	66.3	<0.01
	Hash oil	144	16.8	16.3	81.7	<0.01
	1993–2008	46,211	5.6	5.0	81.7	<0.01

SD, Standard deviation.

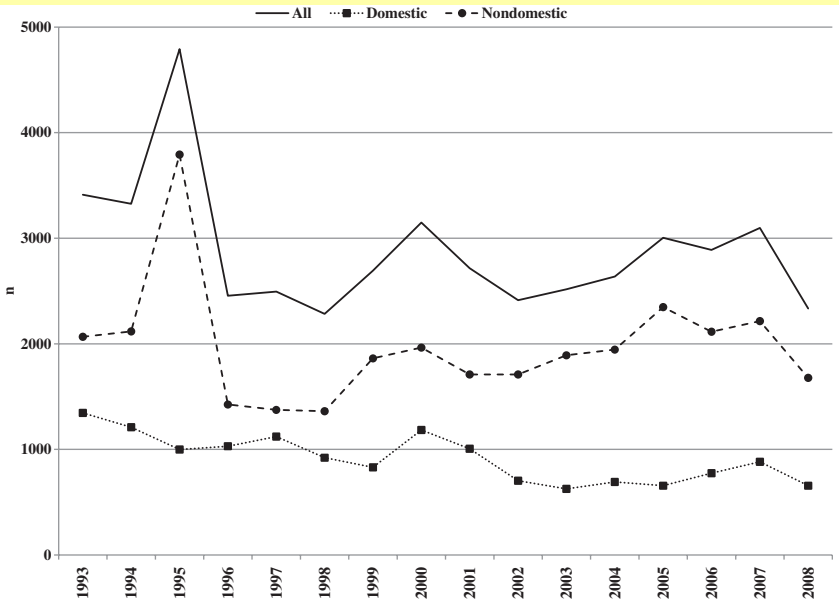

FIG. 4—*Number (*n*) of domestic and nondomestic samples.*

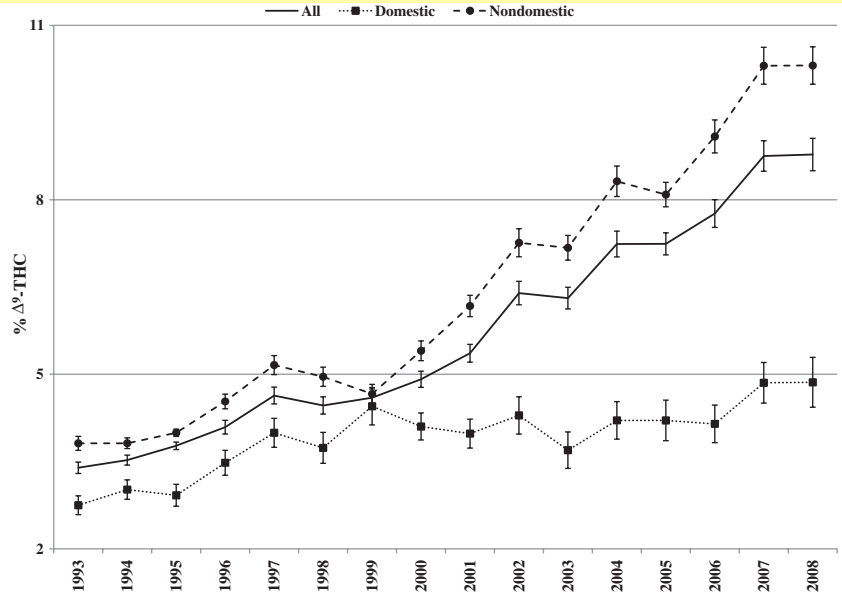

FIG. 5—*Δ^9-THC concentration of domestic and nondomestic samples with 95% confidence intervals.*

TABLE 5—*Mean concentration of minor cannabinoids by type and year.*

	All						Marijuana						Sinsemilla					
Year	THC	CBC	CBD	CBN	CBG	THCV	THC	CBC	CBD	CBN	CBG	THCV	THC	CBC	CBD	CBN	CBG	THCV
1993	3.4	0.2	0.3	0.3	0.0	0.0	3.4	0.2	0.2	0.3	0.0	0.0	5.8	0.2	0.2	0.0	0.1	0.0
1994	3.5	0.2	0.4	0.2	0.1	0.1	3.5	0.2	0.3	0.2	0.1	0.1	7.5	0.2	0.5	0.1	0.3	0.1
1995	3.8	0.2	0.3	0.3	0.1	0.0	3.7	0.2	0.3	0.3	0.1	0.0	7.5	0.3	0.3	0.1	0.3	0.1
1996	4.1	0.2	0.4	0.3	0.2	0.1	3.9	0.2	0.3	0.2	0.1	0.1	9.2	0.3	0.5	0.1	0.4	0.1
1997	4.6	0.3	0.4	0.2	0.2	0.1	4.3	0.3	0.4	0.2	0.2	0.1	11.6	0.3	0.4	0.1	0.5	0.1
1998	4.5	0.2	0.4	0.3	0.2	0.1	4.2	0.2	0.3	0.2	0.1	0.1	12.3	0.4	0.4	0.2	0.5	0.1
1999	4.6	0.2	0.4	0.4	0.2	0.0	4.2	0.2	0.4	0.4	0.2	0.0	13.4	0.3	0.3	0.2	0.5	0.1
2000	4.9	0.2	0.5	0.4	0.2	0.1	4.7	0.2	0.4	0.4	0.2	0.1	12.8	0.2	0.3	0.2	0.4	0.1
2001	5.4	0.2	0.5	0.3	0.3	0.1	5.0	0.2	0.5	0.3	0.2	0.1	9.6	0.2	0.3	0.2	0.4	0.1
2002	6.4	0.2	0.4	0.2	0.2	0.1	5.1	0.2	0.5	0.2	0.2	0.1	11.4	0.3	0.2	0.2	0.3	0.1
2003	6.3	0.2	0.5	0.2	0.3	0.1	5.0	0.2	0.5	0.3	0.3	0.1	11.6	0.3	0.3	0.2	0.4	0.1
2004	7.2	0.3	0.5	0.3	0.3	0.1	5.4	0.2	0.5	0.3	0.3	0.1	11.9	0.3	0.2	0.2	0.5	0.1
2005	7.2	0.3	0.5	0.3	0.4	0.1	5.2	0.3	0.5	0.4	0.3	0.1	11.6	0.3	0.2	0.2	0.4	0.1
2006	7.8	0.2	0.4	0.3	0.3	0.1	5.6	0.2	0.5	0.3	0.3	0.1	11.2	0.3	0.2	0.2	0.4	0.1
2007	8.8	0.3	0.4	0.3	0.4	0.1	6.1	0.2	0.5	0.3	0.3	0.1	11.1	0.3	0.3	0.2	0.4	0.1
2008	8.8	0.3	0.4	0.3	0.4	0.1	5.8	0.2	0.4	0.3	0.3	0.1	11.5	0.3	0.2	0.2	0.4	0.1
1993–2008	5.6	0.2	0.4	0.3	0.2	0.1	4.5	0.2	0.4	0.3	0.2	0.1	11.1	0.3	0.2	0.2	0.4	0.1
SD	5.0	0.3	0.9	0.5	0.3	0.1	3.1	0.2	0.7	0.4	0.3	0.1	6.1	0.4	0.9	0.3	0.4	0.1

	Ditchweed						Hashish						Hash oil					
Year	THC	CBC	CBD	CBN	CBG	THCV	THC	CBC	CBD	CBN	CBG	THCV	THC	CBC	CBD	CBN	CBG	THCV
1993	0.4	0.1	1.7	0.0	0.0	0.0	6.6	0.7	3.8	2.3	0.5	0.3	16.5	0.7	0.1	7.7	0.3	0.5
1994	0.4	0.1	2.0	0.0	0.0	0.0	4.6	0.5	3.5	1.7	0.5	0.2	11.6	0.6	0.2	3.1	0.4	0.5
1995	0.4	0.1	1.6	0.0	0.1	0.0	3.6	0.5	3.3	1.7	0.3	0.1	13.2	1.0	0.7	4.2	0.5	0.3
1996	0.4	0.1	2.1	0.0	0.1	0.0	2.5	0.7	4.5	2.4	0.3	0.1	12.8	1.1	1.3	4.0	0.5	0.5
1997	0.5	0.1	1.9	0.0	0.0	0.0	8.9	0.7	4.0	2.1	0.5	0.3	18.2	1.0	0.3	3.5	0.3	0.6
1998	0.4	0.2	2.0	0.0	0.0	0.0	5.9	0.8	1.7	2.0	0.3	0.2	15.8	0.8	0.2	3.6	0.2	0.5
1999	0.4	0.1	1.8	0.1	0.1	0.0	4.9	0.6	1.8	2.1	0.5	0.3	16.2	1.3	0.4	4.8	0.3	0.4
2000	0.4	0.1	2.0	0.0	0.0	0.0	4.2	0.6	4.9	2.3	0.4	0.1	28.6	1.6	0.5	1.7	0.9	0.7
2001	0.4	0.1	1.8	0.0	0.1	0.0	8.5	0.6	2.7	1.5	0.6	0.3	19.4	1.2	1.3	4.4	0.9	0.6
2002	0.4	0.1	1.5	0.0	0.0	0.0	9.1	0.6	2.5	1.4	0.4	0.2	22.5	0.5	0.3	1.7	1.2	0.3
2003	0.3	0.1	1.8	0.1	0.1	0.0	9.2	0.7	3.9	1.8	0.4	0.2	15.5	0.8	0.2	1.3	0.3	0.4
2004	0.4	0.1	1.5	0.1	0.1	0.0	18.9	0.7	0.8	1.4	0.7	0.2	31.3	1.1	1.1	2.2	1.2	0.4
2005	0.4	0.1	1.9	0.1	0.1	0.0	12.0	0.9	1.7	1.9	0.4	0.2	6.4	0.2	0.3	1.1	0.2	0.2
2006	0.3	0.1	2.4	0.2	0.1	0.0	29.3	0.7	1.6	1.3	0.8	0.2	18.7	0.4	0.1	0.6	0.4	0.1
2007	0.4	0.1	2.0	0.1	0.1	0.0	27.7	0.8	1.2	1.8	1.0	0.3	24.9	0.9	0.6	1.5	0.7	0.3
2008	0.4	0.2	1.9	0.0	0.1	0.0	23.1	0.9	2.1	2.1	0.9	0.4	6.5	0.3	0.2	0.8	0.2	0.1
1993–2008	0.4	0.1	1.8	0.0	0.0	0.0	14.1	0.7	2.5	1.9	0.6	0.3	16.8	0.9	0.5	3.3	0.5	0.4
SD	0.3	0.1	1.5	0.2	0.1	0.0	15.7	0.7	2.9	1.4	0.6	0.3	16.3	0.9	0.8	3.8	0.7	0.4

CBC, cannabichromene; CBD, cannabidiol; CBG, cannabigerol; CBN, cannabinol; Δ^9-THC, Δ^9-tetrahydrocannabinol; THCV, tetrahydrocannabivarin.

is prepared from intermediate type cannabis, hash oil is prepared from drug-type cannabis (high Δ^9-THC and low CBD levels) (3–6,16). CBC and CBN are usually higher in hashish and hash oil samples compared to cannabis samples. The CBN concentration relative to Δ^9-THC reflects the age of the samples (41). CBG content is typically about 3–5% of the Δ^9-THC content; however, in ditchweed this ratio increases to more than 10%, even though this type of cannabis preparation has the lowest overall mean CBG content. This is because ditchweed has very low Δ^9-THC content (0.4% ± 0.3%). THCV, an important biomarker in cannabis (42,43), is generally present at about 0.5–2.5% of the Δ^9-THC content.

Conclusions

The question over the increase in potency of cannabis is complex and has evoked many opinions. The issue has been clouded somewhat by reports of 10- and 30-fold increases in cannabis potency since the 1970s. It is however clear that cannabis has changed during the past four decades. It is now possible to mass produce plants with potencies inconceivable when concerted monitoring efforts started 40 years ago. The PM program has strived to answer this cannabis potency question, while realizing that the data collected in this and other programs have some scientific and statistical shortcomings. These include randomness of samples, correctly identifying the various cannabis products, sampling, natural degradation of Δ^9-THC over time, and different analytical techniques, making comparing results between countries and over time very difficult. However, analysis of the available data in conjunction with the PM program results makes a strong case that cannabis is not only more potent than in the past but also that this high-potency product's market share is also growing. This is clearly evident in the increase in sinsemilla seizures and in the increase in marijuana and sinsemilla samples with Δ^9-THC >9%. The question now becomes: What are the effects of the availability of high-potency products on cannabis users?

Acknowledgments

The authors appreciate the cooperation of the DEA regional laboratories in submitting all the nondomestic samples, and the states' eradication programs for submitting the domestic samples. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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XLR-11 was temporarily made a Schedule I substance by the DEA's emergency scheduling power in May 2013. 78 Fed. Reg. 23735 (May 16, 2013). Shortly before the two-year temporary period was scheduled to expire in May 2015, the temporary scheduling of XLR-11 was extended for an additional year, and the DEA moved to have XLR-11 placed permanently onto the Controlled Substances List. 80 Fed. Reg. 27611 (May 14, 2015); 21 U.S.C. § 811(h)(2). As of this date, XLR-11 is still temporarily scheduled under Schedule I. 21 C.F.R. § 1308.11.

II. Sentencing Guidelines

a. Drug Equivalency [2]

The sentencing issue presented in this case is that XLR-11 is not listed in either the Drug Quantity Table or Drug Equivalency table of § 2D 1.1 of the Guidelines.

When determining the base offense level for a controlled substance not listed in the Guidelines, a court should use "the marihuana equivalency of the most closely related controlled substance referenced in this guideline." 18 U.S.C. § 2D1.1, Application Note 6. In determining the most closely related substance, a court should consider, "to the extent practicable":

> *(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.*
>
> *(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.*

Id.

To determine the "most closely related controlled substance" to XLR-11, I held a hearing on December 11, 2015. At that time, the Government presented testimony from Dr. Jordan Trecki, a pharmacologist with the DEA. The Government argued, with the support of Dr. Trecki, that XLR-11 is most closely related to the controlled substance tetrahydrocannabinol ("THC"). THC is commonly known as the psychoactive ingredient in marijuana.

Hossain presented testimony from Dr. Nicholas Vito Cozzi, a pharmacologist and professor at the University of Wisconsin School of Medicine and Public Health, and Dr. Gregory Dudley, a chemist and a professor at Florida State University. Hossain argued, with the support of Dr. Dudley, that marijuana is the most closely related referenced controlled substance to XLR-11. Additionally, both Doctors Cozzi and Dudley took issue with Dr. Trecki's characterization of THC as the most closely related controlled substance to XLR-11, explaining the flaws in the research that Dr. Trecki relied upon in coming to his conclusions.

Based on the testimony and exhibits presented, I will address each of the Section 2D 1.1 factors in turn.

Factor A—Substantial Similarity: All three experts agreed that, with regards to the first factor, that the chemical structure of XLR-11 is not similar to either marijuana or THC.

Factor B—Efficacy: The second factor to consider is whether the effect of XL11 is substantially similar to the effect of a referenced controlled substance. Dr. Trecki testified that the pharmacological effects of XLR-11 are most similar to THC. (DE 229, Tr. at 29). He explained that synthetic cannabinoids, like XLR-11, activate the

CB1 receptor in the brain, which is the receptor responsible for the psychoactive properties of cannabinoids. (DE 229, Tr. at 67).

Dr. Trecki also testified about the results of a drug discrimination study, which he explained demonstrated that THC and XLR-11 were similar in effect:

> *This is a study where you evaluate animals, where you give them the specific — the test drug, for example THC, and they learn a specific behavior. You then switch out the THC [for another drug] and you observe the behavior . . . So for example, in this case . . . [when animals were given XLR-11] the animals could not differentiate between XLR-11 and the THC.*

(DE 229, Tr. at 68).

Dr. Trecki also compared XLR-11 to THC, explaining that because both XLR-11 and THC are single chemicals, unlike marijuana, XLR-11 is more closely related to THC than marijuana:

> *The marijuana plant, as noted in many published peer review publications, has between 80 and 100 separate cannabinoids in the plant. It has between 500 and 800 different chemicals that make up a living organism in the plant called marijuana. When you look at drugs like XLR-11 . . . these are single manmade chemicals applied to inert, nonpsychoactive vegetable material.*

(DE 229, Tr. at 36).

Finally, Dr. Trecki testified that "the hallucinogenic effects of XLR-11 on the central nervous system are substantially similar to THC." (DE 229, Tr. at 69).

Hossain's experts, Doctors Cozzi and Dudley, both challenged Dr. Trecki's conclusion, and testified that the pharmacological effects of XLR-11 were not necessarily analogous to THC. Dr. Cozzi explained that there were problems with Dr. Trecki's drug discrimination study

that purportedly demonstrates that XLR-11 and THC are similar in effect. Dr. Cozzi opined that the sample size of rodents in the study was smaller than he typically relied on with confidence, and that the results were not reproducible. (DE 229, Tr. at 98, 103).

Further, Dr. Dudley distinguished XLR-11 from THC in effect. He testified that, although XLR-11 binds to the CB1 receptor, as Dr. Trecki had testified, XLR-11 appears to bind more strongly to the CB2 receptor, which is not considered the "psychoactive receptor":

> *A: XLR-11 binds more tightly, more strongly to the CB2 receptor than to the CB1 receptor.*
>
> *Q: In other words, more tightly to the one that would modulate pain as opposed to the one that gets you high; is that a way to say it?*
>
> *A: . . . [T]he one that's primarily located outside of the central nervous system that is not associated with getting you high . . .*

(DE 229, Tr. at 183).

Dr. Dudley further testified that he believes XLR-11 is most closely related to marijuana in effect:

> *Q: When people use marijuana and they get high, they are getting high because the THC?*
>
> *A: That's the consensus, yes.*
>
> *Q: . . . [B]ut marijuana, of course, is separately listed as a schedule one drug, correct?*
>
> *A: Yes.*
>
> *Q: And is marijuana then, in your opinion, appropriate or inappropriate to do the comparison with XLR-11?*
>
> *A: Given that one must choose one of the substances from the guidelines, I think marijuana is appropriate.*

(DE 229, Tr. at 188-89).

Factor C—Potency: The third factor to consider is

whether a lesser or greater amount of XLR-11 is needed to produce a substantially similar effect on the central nervous system as the most closely related referenced substance.

Dr. Trecki testified that a lesser amount of XLR-11 is needed to produce the effects of THC because "XLR acts in an increased manner" over THC. (DE 229, Tr. at 69). In fact, Dr. Trecki testified that, in one study, XLR-11 was "approximately four times as potent as THC." (DE 229, Tr. at 74).

Dr. Cozzi testified that he did not think one could make conclusions about XL11 potency in humans based on studies done on rodents because ". . . the [in] vivo animal studies are not reliable predictors of what a drug will produce in a human being." (DE 229, Tr. at 105). Further, he objected that the data relied on by Dr. Trecki is highly variable and is not reproducible. (DE 229, Tr. at 18). Dr. Dudley similarly testified that there was nothing in the literature that would support finding the XLR-1 l's potency is similar to THC. (DE 229, Tr. at 119).

Based on the testimony I heard on, I find that XLR-11 cannot be easily analogized to THC or to marijuana. While XLR-11 appears to have some of the same psychoactive effects as THC, the chemical structure is unique. The testimony from the experts on the second two factors—efficacy and potency—conflicts. However, because I am instructed by the Guidelines to choose a related substance, I am most persuaded by Dr. Trecki's testimony that the referenced controlled substance XLR-11 most closely relates to is THC. XLR-11, like THC, acts on the CB1 receptor, was found to be similar to THC in one drug discrimination study, and, like THC, is a single chemical,

b. Guideline Range

Once I have determined the most closely related controlled substance referenced in the Guidelines, the

Guidelines instruct that I should use the marijuana equivalency of the related substance to determine the base offense level.

According to the Drug Equivalency Table, the conversion ratio of THC to marijuana is 167:1. Thus, for the purposes of the Guidelines calculation, one gram of marijuana is equal to 167 grams of THC. The amount of XLR-11 that the Government attributes to Hossain, which Hossain did not dispute at the sentencing hearing, was 216 kilograms. Therefore, using the Drug Equivalency Table, Hossain is responsible for 36,072 kilograms of marijuana. This makes Hossain's base offense level 36. (DE 205 at ¶149).

The presentence investigation report filed as to Hossain calculates that Hossain should have eight offense points added to the base offense level: two offense points added pursuant to § 2D1.1(b)(12), another two points added pursuant to § 2D1.1(b)(15)(C), and four points added pursuant to § 3B1.1(a). Hossain also had three points detracted, pursuant to § 3E1.1(a) and § 3E1.1(b). (DE 205 at ¶¶ 50, 51, 53, 57, 58). At the sentencing hearing, I found that Hossain should have an adjustment for role in the offense, but that the adjustment should only be two points, pursuant to § 3B 1.1(c).

Accordingly, Hossain's adjusted offense level is 39, his criminal history category is I, and his resulting Guidelines range is 262 to 327 months of imprisonment.

III. Variance

Although the federal sentencing statute requires that I give consideration to the Guidelines, the sentence should be tailored in light of other concerns. *See Kimbrough v. United States*, 552 U.S. 85 (2007); *United States v. Booker*, 543 U.S. 220 (2005). After *Booker*, there is no presumption that the Guideline sentence should apply, and a variance from the advisory Guidelines may not be presumed unreasonable. *See Rita v. U.S.*, 551 U.S. 338, 351, 354-55 (2007). "A district

judge must include the Guidelines range in the array of factors warranting consideration. The judge may determine, however, that, in the particular case, a within-Guidelines sentence is greater than necessary to serve the objectives of sentencing." *Kimbrough*, 552 U.S. at 91 (internal quotations omitted).

In the context of the crack-cocaine disparity, the Supreme Court in *Kimbrough* upheld a district court's decision to not apply the 100:1 crack-cocaine ratio when the ratio resulted in a sentence that was "greater than necessary" in light of the § 3553(a) factors. *Kimbrough*, 552 U.S. at 92. In fact, the Supreme Court has gone so far as to say in *Spears v. United States* that *Kimbrough* recognized a "district courts' authority to vary from the crack cocaine Guidelines based on *policy* disagreements with them . . ." 555 U.S. 261, 264 (2009). These cases rely on the *post-Booker* discretion of the district court to consider § 3553(a) and vary from the advisory Guidelines when the Guidelines do not fit the instant crime.

Accordingly, I will, and must, consider the § 3553(a) factors in determining whether a Guidelines sentence serves the objectives of sentencing. Factors I should consider under § 3553(a) include: the nature and circumstances of the offense, the history and characteristics of the defendant, and the need for the sentence to provide just punishment, deterrence, incapacitation, and rehabilitation. 18 U.S.C. § 3553(a)(2).

Clearly, this is a serious offense. A 2012 study showed that eleven percent of high school seniors had used synthetic cannabinoids. A recent 2015 study from the same group shows that the number of high school seniors using synthetic cannabinoids had dropped to five percent. *See* Press Release, University of Michigan, Monitoring the Future, "Use of ecstasy, heroin, synthetic marijuana, alcohol, cigarettes declined amount US teens in 2015" (December 16, 2015). This speaks to the need to deter individuals from dealing in these drugs; although on the decline, synthetic cannabinoids

were once relatively commonplace among high schoolers, and dealers should be deterred from distributing these chemicals so that the numbers do not rise again.

According to the DEA's rulemaking in May 2015, there has only been one death tied to XLR-11. 80 Fed. Reg. 27611 (May 14, 2015). However, there have still been increased reports in harm from synthetic cannabinoids more generally and, because the information on synthetic cannabinoids is limited, considering synthetic cannabinoids together may give a more complete picture of the dangers and effects of these drugs. The Government submitted to the Court several articles that discuss case studies of individuals exhibiting complications after they have ingested some type of synthetic cannabinoid. A common trend of these articles shows that individuals who have been hospitalized following synthetic cannabinoid use present kidney injury. *See* DE 217-2, Letter to the Editor from Doctors of Emergency Medicine; DE 217-4, "Acute Kidney Injury Associated with Synthetic Cannabinoid Use—Multiple States, 2012," Morbidity and Mortality Weekly, February 15, 2013.

However, despite the potential dangers of synthetic cannabinoids, and the clear need for deterrence, I believe the Guidelines range for the instant offense fails to achieve the goals of sentencing.

For starters, I am not convinced that THC is a particularly relevant substitute for XLR-11. Based off of the testimony I heard, I believe synthetic cannabinoids need their own category in the Drug Equivalency Chart in order to account for the differences between XLR-11 and THC. But, in the absence of an amendment to the Guidelines, I will use the THC Guideline range as a starting point.

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.*

(DE 229, Tr. at 116-17).

I find this ratio to be better founded than the 1:167 ratio that no one could explain, as it reflects the actual amount of THC in marijuana today. Although I will not rewrite the Guidelines and apply this ratio for THC, this lower ratio is persuasive as to why the current Guideline range fails to provide just punishment for this offense. If I were to use a 1:7 ratio, the amount of XLR-11 Hossain's charged with—216 kilograms—would be equivalent to 1,512 kilograms of marijuana. This would make his base offense level 30 under the Guidelines. When including the adjustments for Hossain's offense level, discussed *supra*, Hossain's sentence range—using an offense level of 33 and a criminal history category of

I—would be 135 to 168 months.

This sentence range is more reasonable than the sentence that the Government suggests I impose, based off the 1:167 ratio. The Government's proposed sentence would mean Hossain starts at the same base offense level as a dealer distributing 167 times more marijuana, a dealer or distributor of 30 to 90 kilograms of heroin, or a dealer or distributor of 150 to 450 kilograms of cocaine. This hardly seems to account for the relative dangers of this crime. Crack cocaine offenses are twice as likely to involve a gun than marijuana offenses. *See* Drug Offenders in Federal Prison: Estimate of Characteristics based on Linked Data, Bureau of Justice Statistics, October 2015. Further, the relative harm from use of XLR-11 does not reach the level of harm from overdoses of cocaine or heroin. As stated previously, the DEA report only lists one known death due to XLR-11. [3] In contrast, in 2014 there were 5,415 reported deaths from cocaine in the United States. *See* "Overdose Death Rates," National Institute of Drug Abuse, December 2015. That same year there were 10,574 reported deaths from heroin in the United States. *Id.*

Additionally, I find the newness of the regulation of XLR-11, as well as the infancy of our understanding of the effects of XLR-11 and other synthetic cannabinoids, to be relevant to determining Hossain's sentence. XLR-11 was first temporarily scheduled in May 2013. In January 2015, Hossain told DEA agents that in 2012, prior to XLR-11 being scheduled, he worked at his father's store where synthetic cannabinoids were sold. Hossain also stated that in May or June of 2012 Hossain and his wife began working at a warehouse that packaged these drugs. All of this conduct occurred prior to XLR-11 being temporarily scheduled and—at least initially—Hossain was unlikely to appreciate the seriousness of his conduct.

Although Hossain was eventually put on notice that XLR-11 was illegal, I find it relevant to Hossain's culpability that XLR-11 was intended to serve as a

replacement for marijuana. Due to the relative infancy of knowledge about synthetic cannabinoids, and XLR-11 in particular, it is unlikely that Hossain or his co-defendants knew the dangers of the synthetic cannabinoids when they were engaged in the instant conduct. If Hossain thought this substance was like marijuana, because it created a high similar to marijuana, he likely believed it posed no more danger than marijuana. Furthermore, Hossain was unlikely to be aware that the substance was, in fact, more dangerous and more severely punished than marijuana. In 2013, the average sentence length of marijuana traffickers was 39 months. *See* Quick Facts: Marijuana Trafficking Offenses, United States Sentencing Commission, 2013. In this case, had I treated XLR-11 as marijuana, Hossain would have been subjected to a sentence of 70 to 87 months.

While I don't find that marijuana is the appropriate substance to compare XLR-11 to—due to the testimony and articles presented about the dangers of XLR-11—I do believe it is relevant when considering whether Hossain appreciated the dangers of the drug with which he was importing. I find that the goals of sentencing, particularly punishment and deterrence, are not achieved by sentencing Hossain to upwards of thirty years in prison for dealing in a substance that was intended to mimic marijuana and so new that only a few years before his arrest it was being sold in gas stations and convenience stores.

Additionally, in considering the other § 3553 factors, I find persuasive that Hossain had no prior criminal history and the instant offense was non-violent.

IV. Conclusion

Although THC is the closest controlled substance to XLR-11 that is currently referenced in the Guidelines, I do not find the Guidelines range for THC particularly helpful in calculating Hossain's sentence. The Guidelines Range yields a sentence that is "greater than

necessary" to achieve § 3553(a)'s purpose. I am dissuaded from sentencing Hossain within the Guideline range because not one expert could provide any scientific basis for the 1:167 ratio for comparing marijuana to THC. Additionally, the nature of this offense, particularly the newness of the regulation of this drug, persuades me that varying downward is necessary. Furthermore, Hossain's lack of any criminal history persuades me that a within-Guidelines range would be "greater than necessary" to achieve any sentencing goals.

Accordingly, for reasons stated in this memorandum and in open court, I sentence Saiful Hossain to 120 months imprisonment, to be followed by three years of supervised release.

DONE AND ORDERED.

FootNotes

1. Other names for synthetic cannabinoids include "K2" and "Spice," which were names given to specific versions of early synthetic cannabinoids. Synthetic cannabinoids are also sometimes referred to as "synthetic marijuana." I use the term "synthetic cannabinoids" to refer generally to these drugs that are used to mimic the high from marijuana.

2. As stated in open court on January 5, 2016, the following Drug Equivalency analysis— as well as my § 3553(a) analysis that relies on a discussion XLR-11—also applies to my sentences of Hossain's co-defendants, Ahmed Maher Elhelw and Ahmed Yehia Khalifa.

3. While Dr. Trecki testified regarding other deaths related to synthetic cannabinoids, it is unclear how many deaths there have been and whether the chemicals present in those cases are similar to XLR-11.

Comment

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EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF LOUISIANA
LAFAYETTE DIVISION

UNITED STATES OF AMERICA Plaintiff, v. THOMAS WILLIAM MALONE, JR. Defendant.	:	Case No.: 6:12-CR-00146-EEF-PJH

DECLARATION OF NICHOLAS V. COZZI, Ph.D.

I. My name is Nicholas Vito Cozzi. I am currently a scientist and educator in the Department of Cell and Regenerative Biology at the University of Wisconsin School of Medicine and Public Health in Madison, WI. I hold a B.S. degree in Pharmacology and Toxicology and a Ph.D. degree in Pharmacology from the University of Wisconsin School of Pharmacy. I teach Medical Pharmacology to second-year medical students and I teach various courses in Pharmacology and Toxicology to undergraduate students, M.D. and Ph.D. students, pharmacy students, and veterinary students.

II. I have approximately 29 years of research experience in the design, chemical synthesis, and pharmacological testing of novel compounds. My research involves the design, chemical synthesis, and pharmacological testing of substances with central nervous system activity, especially those with psychostimulant, hallucinogenic, and antidepressant effects. My laboratory is interested in how these agents act in the brain to affect awareness, cognition, and mood, and in their clinical value for treating addiction, anxiety, depression, post-traumatic fear, and other mental health ailments. I have published the results of my research in international peer-reviewed scientific journals beginning in 1991 and continuing through the present. My qualifications and experience are detailed in my curriculum vitae, which is attached.

III. I have been asked to comment on certain statements made by Jordan Trecki, Ph.D., a pharmacologist employed by the Drug Enforcement Administration, regarding the compound known as AM-2201*, and render my own opinions on AM-2201. In particular, my comments relate to written and oral testimony given by Dr. Trecki in the sentencing hearing in the United States District Court for the District of Minnesota in U.S. v. Carlson (Case #12-CR-305).

* AM-2201 is identified as (1-(5-fluoropentyl)-3-(1-naphthoyl)indole).

IV. It is Dr. Trecki's opinion that 1) AM-2201 is pharmacologically "most closely related" to delta 9-tetrahydrocannabinol (THC) and 2) "AM2201 is at least as potent, if not more potent than THC, supporting a potency ratio of 1:1." Dr. Tecki's makes the following statements to support his opinion.

A. Dr. Trecki: "AM2201 has a hallucinogenic effect on the central nervous system that is substantially similar to THC."

1. Neither AM-2201 nor THC is accurately described as a "hallucinogen" under any current scientific or medical classification scheme.

i. It is widely held among pharmacologists, medical doctors, and other professionals that the term "hallucinogen" refers to drugs whose primary effects resemble the effects produced by mescaline, psilocybin, and lysergic acid diethylamide (LSD); another term for these substances is "psychedelic" (Nichols, 2004). No pharmacologist or medical professional, or even the casual user, would claim that THC mimics the effects of LSD. There is no evidence that AM-2201 does so either.

ii. Many drugs can produce hallucinations as a side-effect in some individuals. For example, the Attention Deficit Hyperactivity Disorder drug amphetamine (Adderall®), the anti-Parkinson's disease drugs levodopa (Larodopa®) and pramipexole (Mirapex®), and the anti-HIV drug efavirenz (Sustiva®) can produce hallucinations at normal, recommended doses. However, none of these drugs are correctly classified as "hallucinogens".

2. No systematic studies are available in the scientific literature that qualify or quantify the psychoactive effects of AM-2201 in humans either by itself or in comparison to THC.

i. A controlled metabolic study in which a single volunteer consumed an oral dose of 5 mg AM-2201 reported no physical or mental effects at any stage of the experiment, even though the substance was detectable in the blood and urine (Hutter et al., 2013). In contrast, oral doses of THC as low as 2.5 mg are associated with a variety of physical and psychotropic effects such as dry mouth, reddening of the eyes, euphoria, dizziness, memory impairment, analgesia, and sleepiness, among others (http://www.rxabbvie.com/pdf/marinol_PI.pdf). At a minimum, these data suggest that THC is at least 2-fold more potent than AM-2201 when taken orally, but it is likely that the oral potency ratio of THC to AM-2201 is much higher.

ii. The lack of psychoactivity of oral AM-2201 is very likely due to extensive metabolism in the gastrointestinal tract and liver, a phenomenon known as the "first-pass" effect.

iii. There are no study data available that describe the effect or potency of AM-2201 when administered by any other routes. Some other potential routes of ingestion include inhalation of vaporized or aerosolized material, sublingual absorption, intravenous or intramuscular injection, or transdermal absorption.

iv. There exist numerous literature reports of subjects in whom varying levels of AM-2201 was detected *post hoc* (e.g., following a traffic stop) (Alhadi et al., 2013; Kronstrand et al., 2013; Rodrigues et al., 2013; Yeakel and Logan, 2013; Elian and Hackett, 2014; Kim et al., 2014; Musshoff et al., 2014). However, it is not possible to establish a dose-related effect of AM-2201 from these reports because the routes of administration are unknown, no uniform sample collection times were adhered to, and the levels of AM-2201 detected in these persons varied by over 400-fold.

v. Because "potency" refers to the size of a dose or the concentration of a drug required to produce a specific effect, and because there are no studies establishing a specific dose-related effect of AM-2201, it is erroneous to make the assertion that AM-2201 "is at least as potent, if not more potent than THC," as claimed by Dr. Trecki.

vi. It is certain, at least, that any psychoactive or physiological effects produced by AM-2201 are highly dependent on the route of administration, with oral doses being completely inactive, whereas oral doses of THC are fully active. Thus, any potency comparison between AM-2201 and THC that does not take into account the route of administration is faulty.

B. Dr. Trecki: "Data from *in vitro* receptor binding studies demonstrate that both AM2201 and THC bind to the cannabinoid 1 (CB1) receptor."

1. It is well known that data from *in vitro* binding experiments are not sufficient to conclude what effect, if any, a substance will have in humans.

2. The fact that two substances bind to the same receptor does not indicate that they will have similar biological effects. For example, the substances acetylcholine and atropine have very different biological effects, even though they both bind to the same (muscarinic) receptor.

3. An ingested drug substance must reach its site of action in the body in sufficient quantity or concentration to produce a pharmacological effect; all drugs exhibit a threshold concentration below which they are inactive.

4. *In vitro* binding experiments are conducted in isolated cell or tissue preparations. They are intentionally designed to exclude biological processes such as absorption, distribution, metabolism, and excretion (collectively known as *pharmacokinetics*). These processes determine the quantity and concentration of a substance reaching a

biological target, for example, brain tissue. Thus, pharmacokinetic processes govern whether a drug will attain the minimum threshold required to produce a psychoactive effect or a physiological response.

5. The absence of any physical or psychotropic effect when 5 mg AM-2201 was ingested by mouth (Hutter et al., 2013) is a case in point in demonstrating the importance of the pharmacokinetic processes described above in determining the ultimate effects (or lack thereof) of a drug; the fact that oral AM-2201 is inactive demonstrates the limitations of relying on binding data to reach conclusions regarding the activity of a drug. If one disregards human pharmacokinetic processes, one will reach an erroneous conclusion regarding the activity and potency of AM-2201.

6. Therefore, while *in vitro* binding experiments can yield useful information about biological drug targets, they are not designed to answer, and cannot establish, whether a substance will have a biological effect at all, the nature of its effect, or whether the substance will reach its site of action in sufficient quantity or concentration to produce a response. One cannot conclude from *in vitro* binding data that a compound will produce a response in a human being.

C. Dr. Trecki: "Data from *in vitro* functional assays demonstrate that both AM2201 and THC activate CB1 receptors and thus act as agonists at the CB1 receptor. Agonist activation of the CB1 receptor leads to psychoactive and physiological actions."

1. Here, Dr Trecki tries to draw a conclusion regarding psychological and physiological responses (which can *only* occur in an intact animal) from *in vitro* data. Again, it is well known that data from *in vitro* assays do not allow one to conclude what effect, if any, a substance will have in an intact organism. As discussed above, an ingested substance must reach its site of action in sufficient quantity or concentration to produce a behavioral effect. This information is simply unobtainable from an *in vitro* assay.

2. *In vitro* functional assays typically measure biochemical or electrophysiological phenomena while deliberately excluding pharmacokinetic processes. These processes determine whether or not a drug will have an observable effect. Without considering pharmacokinetic processes, it is erroneous to draw any conclusions regarding the supposed psychological or physiological activity of a drug in an intact human being.

3. Thousands of compounds are known which show functional agonist activity *in vitro*, only to be shown later to be completely inert in humans. Hence, Dr. Trecki's conclusion that "Agonist activation of the CB1 receptor leads to psychoactive and physiological actions" is erroneous and premature. The observation of functional activity in an *in vitro* study may allow one to formulate hypotheses about biological or psychological effects in humans, but these conjectures must ultimately be tested by experiment.

4. The biochemical signaling cascades, which are studied in *in vitro* functional assays, are not understood well enough to predict specific psychoactive effects.

5. *In vitro* functional assays, like *in vitro* binding assays, are not designed to answer, and cannot establish, whether a substance will have a biological or psychological effect at all, the nature of its effect, or whether the substance will reach its site of action in sufficient quantity or concentration to produce an observable response. One cannot draw a conclusion about whole-person responses from *in vitro* data.

D. Dr. Trecki: "Data from *in vivo* studies (drug discrimination tests) demonstrate that AM2201 has subjective effects that that are substantially similar to the effects of THC."

1. Despite an exhaustive search of the peer-reviewed scientific literature, including sources such as PubMed, MedLine, and the Library of Congress, no drug discrimination studies were found to support Dr. Trecki's statement. There are no scientific or medical publications comparing the subjective effects of AM-2201 to those of THC.

   i. Here, it appears that Dr. Trecki refers to *unpublished* data obtained from Dr. Michael Forster and Dr. Michael Gatch from the University North Texas, which he used in oral testimony at the sentencing hearing in the United States District Court for the District of Minnesota in U.S. v. Carlson (Case # 12-CR-305). In his testimony, Dr. Trecki admits that none of the drug discrimination studies that he relies on have been published in the scientific literature.

   ii. Dr. Trecki contends that "The results of the drug discrimination assays, they have been peer reviewed. The researchers at the University of Texas that originally did the research peer reviewed their own work." It appears that Dr. Trecki does not fully comprehend the meaning of the phrase "peer review". By definition, peer review is an evaluation conducted by *peers* (i.e., other experts), not oneself. The whole point of peer review is to obtain an *anonymous*, *independent* critique and evaluation of one's work—it is not scientifically acceptable to claim that scientists "peer reviewed their own work". This critical step in the scientific publication process is meant to ensure that the experimental methods and resulting data are sound and that the conclusions are supported by the experimental results, thereby lending credence to the study.

   iii. Both Drs. Forster and Gatch are well-respected scientists with experience and publications in the areas of behavioral pharmacology, including drug discrimination. Nonetheless, their drug discrimination work on AM-2201 has yet to be validated through the peer review process. It is scientifically unacceptable to cite unpublished work until other scientists with the expertise to critique the studies have validated it.

2. While there exists much literature showing that drug discrimination studies in animals can indeed separate drugs into classes which have similar effects in humans, including drugs with THC-like effects, there are important exceptions and limits to the drug discrimination approach. Rat drug discrimination tests are not always reliable.

    i. Data from animal drug discrimination assays may produce "false positives" regarding subjective effects in humans. For example, the drugs lisuride, quipazine, and yohimbine are three drugs that are known NOT to be hallucinogenic in humans. However, these three drugs substitute for the hallucinogen LSD in rat drug discrimination assays (Appel et al., 2004). Thus, drug discrimination assays conducted in nonhuman animal subjects can lead to erroneous conclusions. False positive results cast doubt on the reliability of such assays to predict whether the "subjective effects" of two drugs in animals "are substantially similar" to drug effects, if any, produced in human beings.

    ii. Likewise, while discriminative stimulus effects of THC often exhibit a high degree of pharmacological specificity, there is not always a correspondence between THC-like stimulus effects in rats and a drug's ability to produce a THC-like intoxication in humans.

        a. Drugs that produce psychoactive effects that are unlike THC in humans can nevertheless produce THC-like responses in rats. For example, MDMA, diazepam, and pentobarbital partially or fully substitute for THC in animal drug discrimination tests (Mokler et al., 1986; Barrett et al., 1995). These drugs are not perceived to be THC by human beings.

        b. On the other hand, some compounds that are known to produce THC-like effects in humans fail to substitute for THC in rats (Hollister, 1974; Balster and Prescott, 1992).

E. In his testimony in U.S. v. Carlson, Dr. Trecki states "In the absence of human data, it would be inappropriate to administer these type of drugs to human patients for the reasons of there are no accepted medical uses for these drugs in the United States."

1. Dr. Trecki is misinformed. There are numerous ongoing clinical trials involving natural and synthetic cannabinoids presently occurring in the United States and elsewhere around the world. Accepted medical uses are *only* determined through clinical testing in humans. In fact, laws enacted by the Congress of the United States *require* drug testing in humans to assess safety and efficacy before a drug can be approved for clinical use. This testing is regulated and reviewed by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, whose mission is to ensure that drugs marketed in the United States are safe and effective.

2. Dr. Trecki states "In addition, the adverse effects experienced by multiple people as reported in either case reports or poison control centers demonstrate that this would not be appropriate to give to a human. There's no medical purpose for it, and the adverse effects are quite serious."

    a. There are numerous medical purposes for which natural or synthetic cannabinoids are being developed (Pacher et al., 2006) and there are literally hundreds of ongoing or completed clinical trials involving these substances. Some of these FDA- and DEA-approved studies include clinical trials for anticancer activity, antiemetic effects, appetite stimulation, analgesia, antianxiety effects, insomnia, antiseizure activity, inflammatory bowel disease, multiple sclerosis, fibromyalgia, obesity, and many other psychological and physical ailments. *See* www.clinicaltrials.gov, a Web site maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) for a listing.

    b. All currently FDA-approved drugs can produce adverse effects; the potential of a substance to produce adverse effects in no way precludes clinical trials with that substance.

F. Dr. Trecki claims: "AM2201 has a potency ratio of 1:1 with THC that is based upon data demonstrating that AM2201 is at least as potent (≥) as THC."

1. "Potency" refers to the size of a dose or the concentration of a drug required to produce a specific effect. The statement by Dr. Trecki does not indicate exactly what drug effect is being measured nor does he provide any data used to calculate the "potency ratio".

V. According to the sentencing documents in U.S. v. Carlson, AM-2201 has been made equivalent to JW-018 (identified as [1-pentyl-3-(1-naphthoyl)indole]), which is then made equivalent to THC for sentencing purposes.

A. I have been unable to locate any published studies that compare the potency of AM-2201 to JW-018.

B. According to the U.S.S.C. § 2D1.1, n.8(D), 1 gram of THC, whether synthetic or organic, is made equivalent to 167 grams of marihuana.

1. The THC content calculated by this guideline and expressed as a THC percent = 1/167 x 100 = 0.6%. Marihuana with a THC percent of less than 1% is called "ditchweed" or "hemp" and is used for manufacturing (e.g., hemp cloth, hemp rope) or in the food industry (e.g., hemp seed oil, hemp protein) (Holler et al., 2008).

C. The 1:167 multiplier does not accurately reflect the actual THC content of contemporary marijuana that is used for medicinal or psychoactive purposes. The multiplier artificially inflates the severity of a punishment by using an implausibly low marijuana THC content.

1. The National Institute on Drug Abuse maintains a marijuana Potency Monitoring Program directed by Dr. Mahmoud A. ElSohly at the National Center for Natural Products Research at the University of Mississippi School of Pharmacy, University, MS. This program provides analytical potency data for marijuana seized in the United States.

2. According to the Potency Monitoring Program test results, marihuana cultivated for psychoactive effects had a THC content in the 3.4-5.8% in 1993. The THC content increased to over 14.5% by 2013. (Mehmedic et al., 2010; Botticelli, 2014).

3. Therefore the sentencing guideline *miscalculates* the actual THC content of present-day marihuana by about 24-fold (14.5/0.6), resulting in a **multiplier that is at least 24-fold too high**. The multiplier, adjusted for actual present-day THC content, would be about 1:7, not 1:167.

VI. Summary

A. Dr. Trecki's conclusions about AM-2201 are based on extrapolations from *in vitro* experiments and unvetted animal data. Such data are not accepted by the scientific community to be a sufficient basis from which to draw conclusions regarding drug responses in human beings. In fact, over 90% of potential new drugs are not approved by the FDA for human use, in large part because of the failure of *in vitro* and animal testing to reliably predict drug effects in humans (DiMasi et al., 2003). At best, Dr. Trecki's speculations could form the basis of a hypothesis that could then be rigorously tested in humans with the proper safeguards in place.

B. The 1:167 sentencing multiplier appears to be arbitrary and capricious. It is not based on the actual THC content of today's pharmacologically active marijuana.

Recoverable Signature

X

Nicholas Vito Cozzi, Ph.D.

Signed by: Nicholas V. Cozzi

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EDUCATION

Ph.D., Pharmacology **1994**
University of Wisconsin-Madison School of Pharmacy
Doctoral Thesis: *Pharmacological Studies of Some Psychoactive Phenylalkylamines: Entactogens, Hallucinogens, and Anorectics*

B.S., Pharmacology and Toxicology **1988**
University of Wisconsin-Madison School of Pharmacy

AWARDS AND GRANTS

Neuropharmacology Research Grant, Usona Institute **2011 – Present**

Wisconsin Medical Alumni Association Distinguished Basic Science Teaching Award **2013**

University of Wisconsin Professional Development Grant **2008 – 2009**

National Institute on Drug Abuse Grant DA017675 **2004 – 2007**

Brody Basic Science Incentive Award, Brody School of Medicine, East Carolina University **2001 – 2002**

Excellence in Teaching Award, Brody School of Medicine, East Carolina University **2000**

Brain and Behavior Research Foundation (formerly NARSAD) Young Investigator Award **1997 – 2000**

TEACHING EXPERIENCE

Visiting Professor: Human Services 1130 (undergraduate course) **2011 – Present**
College of DuPage, Glen Ellyn, IL
Topic: Molecular and cellular mechanisms of psychedelic drug action

Lecturer: Molecular Principles in Pharmacology (graduate course) **2011 – 2013**
University of Wisconsin School of Medicine and Public Health, Madison, WI
Topics: General principles, drug disposition, autonomic and neuromuscular drugs, central nervous system agents, autacoid pharmacology

Course Director, Lecturer: Medical Pharmacology (Foundations of Medicine 1-4; professional/graduate courses) **2007 – Present**
University of Wisconsin School of Medicine and Public Health, Madison, WI
Topics: General principles, drug disposition, autonomic and neuromuscular drugs, cardiovascular and blood drugs, central nervous system agents, gastrointestinal drugs, chemotherapeutics, autacoid pharmacology, endocrine drugs, botanicals, toxicology, immunopharmacology, therapeutic drug monitoring, drug interactions

Lecturer: Laboratory Techniques in Pharmacology and Toxicology (graduate course) **2007 – Present**
University of Wisconsin School of Pharmacy, Madison, WI
Topic: Pharmacology of neurotransmitter uptake transporters

Visiting Professor: Foundations of Psychedelic Studies (undergraduate course) **1986 – Present**
Northern Illinois University, DeKalb, IL
Topic: Pharmacology of psychedelic agents

Lecturer: Basic and Clinical Veterinary Therapeutics (professional course) **2009**
University of Wisconsin School of Veterinary Medicine, Madison, WI
Topics: Pharmacotherapy of pancreatic, adrenal, and thyroid disorders

Course Director, Lecturer: Physiology in Pharmacology (graduate course) **2008 – 2011**
University of Wisconsin School of Medicine and Public Health, Madison, WI
Topics: Homeostasis, cell structure, movement across membranes, neuronal signaling, sensory physiology, brain, muscle, endocrine, reproduction, cardiovascular system, pulmonary, renal, gastrointestinal, metabolism, immunology

Course Director, Lecturer: Pharmacology (professional course) **2005 – 2007**
Carroll University, Waukesha, WI
Topics: General principles, drug disposition, autonomic and neuromuscular drugs, cardiovascular and blood drugs, central nervous system drugs, gastrointestinal drugs, chemotherapeutics, autacoid pharmacology, endocrine drugs, botanicals, toxicology, drug interactions

Lecturer: Physiological Proteogenomics (graduate course) **2003 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topic: Applications of proteome analysis to drug development and toxicology

Course Director, Lecturer: Pharmacology Seminar (graduate course) **2001 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

Lecturer: Molecular Pharmacology (graduate course) **2000 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: Receptor kinases, neurotransmitter transporters, cell adhesion molecules, site-directed mutagenesis, chimeras, positron emission tomography

Course Director, Lecturer: Laboratory Research Techniques (graduate course) **2000 - 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: Neurotransmitter transporter assays, cell culture techniques, polymerase chain reaction

Lecturer: Central Nervous System Pharmacology (graduate course) **1999 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: Neurotransmitter receptors, gene knockouts, synaptic vesicle storage and release mechanisms

Lecturer: Cellular and Molecular Neuroscience (graduate course) **1999 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: Neurotransmitter receptors, neurotransmitter transporters

Lecturer: Medical Pharmacology (professional/graduate course) **1998 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC
Topics: General principles, receptor mechanisms, dose-response relationships, absorption, distribution, metabolism, excretion, pharmacokinetics, drug interactions

Lecturer: Pharmacology (professional course) **1995 – 1998**
University of Wisconsin School of Pharmacy, Madison, WI
Topic: Cardiovascular pharmacology

Lecturer: Environmental Toxicology (graduate course) **1994 – 1998**
Center for Environmental Toxicology, University of Wisconsin-Madison, Madison, WI
Topics: Neurotoxicology, gastrointestinal toxicology

Teaching Assistant: Pharmacy curriculum (various undergraduate Pharmacy courses) **1989 – 1994**
University of Wisconsin School of Pharmacy, Madison, WI

Graduate Students
Dr. LuAnn Cuthbertson-Lucas; received Ph.D. 2001
Dr. Kevin Foley; received Ph.D. 2002
Dr. Kevin DeSanty; received Ph.D. 2002
Dr. Jessica Gaskey-Sharpe; received Ph.D. 2004

PUBLICATIONS

Refereed

JS Bonano, ML Banks, R Kolanos, F Sakloth, M Barnier, RA Glennon, **NV Cozzi**, JS Partilla, MH Baumann, SS Negus. Abuse-related neurochemical and behavioral effects of para-substituted methcathinone analogs in rats. I. Quantitative structure-activity relationship (QSAR) analysis. *Brit. J. Pharmacol., (submitted)*

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C Leckie, BE McKay, **NV Cozzi**, PE Mallet. Candidate for abuse: acute effects of the "bath salts" constituent 4-methylmethcathinone (mephedrone, 4-MMC). *Southern Ontario Neurosci. Assoc. Abs., 33*, A23, 33rd Annual Conference, Wilfrid Laurier University, Waterloo ON, N2L 3C5 (2013)

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NV Cozzi, TA Mavlyutov, MA Thompson, AE Ruoho. Indolethylamine *N*-methyltransferase expression in primate nervous tissue. *Soc. Neurosci. Abs., 37*, 840.19 (2011)

MH Baumann, JS Partilla, MA Ayestas, Jr., RB Rothman, **NV Cozzi**. Designer methcathinone analogs target dopamine and serotonin transporters in rat brain. *Soc. Neurosci. Abs., 37*, 472.14 (2011)

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JA O'Connor, LH Lapczynski, AJ Dahly-Vernon, YA Evrard, DL Evans, AL Wittenburg, SK Korb, SH Nye, HJ Vernon, **NV Cozzi**, HJ Jacob, RJ Roman. Delay in the progression of diabetic nephropathy in the T2DN rat. *Amer. Diabetes Assoc. 66th Annual Scientific Sessions*, 2185-PO (2006)

JA O'Connor, AL Wittenburg, MF Perrine, LH Lapczynski, DL Evans, YA Evrard, SK Korb, AJ Dahly-Vernon, HJ Vernon, SH Nye, **NV Cozzi**, HJ Jacob, RJ Roman. Diabetes-induced nephropathy in the T2DN rat. *Amer. Diabetes Assoc. 66th Annual Scientific Sessions*, 773-P, (2006)

YA Harrington, SK Korb, **NV Cozzi**, SH Nye, AL Wittenburg, HJ Vernon, DL Evans, JA O'Connor, LH Lapczynski, AJ Dahly-Vernon, JF Baye, RJ Roman, HJ Jacob. Using PharmGenix rats to detect tacrine hepatotoxicity. *Clin. Pharmacol. Ther., 79*, P82 (2006)

NV Cozzi, D Marona-Lewicka, DE Nichols, A Gokin, KF Foley. Novel aminopropiophenones as antiobesity agents. *Soc. Neurosci. Abs., 31*, 533.5 (2005)

SH Nye, **NV Cozzi**, JF Baye, DL Evans, YA Evrard, SK Korb, JA O'Connor, HJ Vernon, AL Wittenburg, M Hessner, X Wang, HJ Jacob, RJ Roman. Does the lack of genetic diversity in animal models currently used for safety testing put the public at risk? *FDA Science Forum Abs.*, 305 (2005)

KF Foley, RA Galbraith, A Gokin, **NV Cozzi**. Novel aminopropiophenones as antiobesity agents. *Exp. Biol. Abs.*, *19*, 85.10 (2005)

SH Nye, **NV Cozzi**, JF Baye, AL Wittenburg, SK Korb, YA Evrard, RJ Roman, HJ Jacob. Improved rat models for predictive toxicology. *Soc. Toxicol. Abs., 44*, 1897 (2005)

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DM Raffel, W Chen, DL Gildersleeve, YW Jung, **NV Cozzi**. Transport of [^{11}C]meta-hydroxyephedrine, [^{11}C]-epinephrine, and biogenic amines by the human norepinephrine transporter. *J. Nucl. Med., 45*, 216P (2004)

NV Cozzi, KF Foley. Stimulant and antidepressant-like effects of novel arylketones. *Soc. Neurosci. Abs., 29*, 757.11 (2003)

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KF Foley, ME Van Dort, **NV Cozzi**. Stereochemical effects of *meta*-hydroxyephedrine isomers at monoamine uptake transporters: a structure-activity study. *Soc. Neurosci. Abs., 26*, 819.20 (2000)

NV Cozzi, KF Foley. Bromine substitution at the ring 3- or 4-position of methcathinone enhances potency at serotonin uptake transporters. *Soc. Neurosci. Abs., 25*, 678.17 (1999)

NV Cozzi, MK Sievert, AT Shulgin, P Jacob III, AE Ruoho. Methcathinone and 2-methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one (methylone) selectively inhibit plasma membrane catecholamine reuptake transporters. *Soc. Neurosci. Abs., 24*, 341.8 (1998)

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A Boileau, **NV Cozzi**, P Chen, C Czajkowski. Identification of GABA- and diazepam-responsive regions of the $GABA_A$ receptor using $\gamma 2/\alpha 1$ subunit chimeras. *Soc. Neurosci. Abs., 22*, 509.3 (1996)

MH Weiler, D Katz, H.-J Lee, **NV Cozzi**, K Das Gupta. Inositol phosphate (IP) accumulation in rat neostriatal slices under conditions used to monitor neurotransmitter release. *Soc. Neurosci. Abs., 17,* 173.9 (1991)

Invited Reviews and Other Publications

NV Cozzi. Psychedelic breakthroughs in neuroscience: how psychedelic drugs influenced the growth and development of psychopharmacology. *Multidisc. Assoc. Psychedelic Studies, 23 (1)*, 16-19 (2013)

Editor: *The Shulgin Index*, AT Shulgin, PF Daley, T Manning (2011). Transform Press, Berkeley, CA 94712. ISBN: 978-0-9630096-3-0

Book review: *Psychedelic Medicine: New Evidence for Hallucinogens as Treatments*, TB Roberts, MJ Winkelman, Eds. (2007) Praeger/Greenwood, Westport, CT 06880. ISBN: 0-275-99023-0

RA Sewell, M Baggott, **NV Cozzi**, R Doblin, R Forte, M Franklin, NM Goldsmith, P Goodwin, C Guillot, J Hanna, J Holmes, I Jerome, S Kumar, CD Lovett, D Merkur, J Onnie-Hay, E Peden, TB Roberts, MA Ruderman, K Sachs, TC van Veen. So you want to be a psychedelic researcher? *The Entheogen Review, 15*, 41-47 (2006)

Contributing Editor: *Psychedelics* in *Alterations of Consciousness: An Empirical Analysis for Social Scientists*, I Baruss (2003). American Psychological Association Books, Washington, DC 20002. ISBN: 1-557-98993-1

NV Cozzi. SB-207266, an orally active 5-HT_4 receptor antagonist for the treatment of irritable bowel syndrome. *Curr. Res. Serotonin, 3*, 115-118 (1998)

Contributing Editor: *Peyote and the Native American Church* in *Peyote*, N Ross-Flanigan (1997). Berkeley Heights, NJ 07922. ISBN: 0-8949085-1-0

Contributing Editor: *Toxicity of Ecstasy* in *Ecstasy Reconsidered*, N Saunders (1997). Turnaround Press, London, England. ISBN: 0-9530065-0-6

NV Cozzi. SDZ-HTF-919, a 5-HT_4 receptor partial agonist for the treatment of gastrointestinal motility disorder and irritable bowel syndrome. *Curr. Drugs Serotonin ID Res. Alert, SDZ-HTF-919,* ISSN 1361 6285 (1997)

NV Cozzi. A review of the chemistry and pharmacology of CV-5197, a 5-HT_2 receptor antagonist. *Curr. Drugs Serotonin ID Res. Alert, CV-5197,* ISSN 1361 6285 (1997)

NV Cozzi. Effects of water filtration on marijuana smoke: a literature review. *Multidisc. Assoc. Psychedelic Studies, 4, (2),* 4-6 (1993)

SERVICE

Peer reviewer for the following scientific journals:
Archives of Toxicology
Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry Letters
CNS Neuroscience & Therapeutics
Drug Testing and Analysis
Journal of Neurochemistry
Journal of Neural Transmission
Psychopharmacology

Educational Policy Council **2007 – 2010**
University of Wisconsin School of Medicine and Public Health

Year 2 Course Directors' Committee for the accreditation report to the Liaison Committee on Medical Education (LCME) **2009**
University of Wisconsin School of Medicine and Public Health

Medical Students Committee report to the Liaison Committee on Medical Education (LCME) **2009**
University of Wisconsin School of Medicine and Public Health

Year 2 Grading Subcommittee co-chair, Educational Policy Council **2009**
University of Wisconsin School of Medicine and Public Health

Year 2 Curriculum Steering Committee **2008 – 2009**
University of Wisconsin School of Medicine and Public Health

Research Proposal Reviewer **2001**
Dept. of Veterans Affairs, Office of External Reviews, Neurobiology-D
VA Palo Alto Healthcare System-Livermore Division, Livermore, CA

Neuroscience Steering Committee **2000 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

Neuroscience Symposium Organizing Committee **2000 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

Neuroscience Doctoral Program Curriculum Committee **2000 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

United States Pharmacopeial Convention (USP) **2000**
Quinquennial Meeting 2000 Alternate Delegate

Consulting Editor*: Journal of Drug Education and Awareness* **1999 – 2004**

Telemedicine Distance Learning Committee **1999 – 2004**
Brody School of Medicine, East Carolina University, Greenville, NC

Judge: Carol Volkman Awards, Doctoral Student Research Day **1999 – 2000**
Brody School of Medicine, East Carolina University, Greenville, NC

PRESENTATIONS AND PROFESSIONAL ACTIVITIES

Hofmann's Potion **October 20, 2014**
Presentation with Thomas Roberts, Ph.D., Bruce Sewick, M.A., Connie Littlefield
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

Neurons to Nirvana: Understanding Psychedelic Medicines **April 7, 2014**
Presentation with Thomas Roberts, Ph.D., Bruce Sewick, M.A., Oliver Hockenhull
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

Psychedelics: Science and Spirit **November 16, 2013**
Presentation, Chicago Consciousness Café, Chicago, IL

Molecules, Mind States, and Mystical Experiences-Insights from the Study of Psychedelics **November 16, 2013**
Presentation with Thomas Roberts, Ph.D. and Bruce Sewick, M.A.
Sponsored by the College of DuPage, Glen Ellyn, IL

Psychedelics: Science and Spirit; DMT: The Spirit Molucule **November 11, 2013**
Presentation with Natlie Metz, N.D. and Mitch Schultz
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

A Psychedelic Conversation: Pharmacology, The Shulgin Farm Report, Creativity and Problem Solving **April 29, 2013**
Presentation with Paul Daley, Ph.D. and James Fadiman, Ph.D.
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

Indolethylamine *N*-methyltransferase expression in primate nervous tissue. **April 19, 2013**
Presentation, Psychedelic Science 2013, Oakland, CA

Psychedelics in the 21st Century: Pharmacology of Psychedelic Agents **November 3, 2012**
Presentation, College of DuPage, Glen Ellyn, IL

Psychedelics: Breakthroughs in Neuroscience, Therapeutics, and Humanitites **May 7, 2012**
Presentation with Thomas Roberts, Ph.D. and Bruce Sewick, M.A.
Sponsored by the Wisconsin Union Directorate, University of Wisconsin-Madison

Molecular and Cellular Principles of Psychedelic Drug Action **December 12, 2011**
Presentation and workshop, Cartographie Psychedelica, Oakland, CA

Is *N,N*-Dimethyltryptamine (DMT) a Neurotransmitter? **October 17, 2010**
Presentation, Chicago Consciousness Café, Chicago, IL

Recent Developments in *N,N*-Dimethyltryptamine (DMT) Pharmacology **April 16, 2010**
Presentation, Psychedelic Science in the 21st Century, San Jose, CA

Enhancing the Professional Culture of Schools of Medicine: Relationship-Centered Care Initiative Immersion Conference II **May 22-25, 2007**
Indiana University School of Medicine and Regenstrief Institute, Indianapolis, IN

NIH Summit Workshop on Predictive Toxicology — **June 15-17, 2004**
National Institutes of Health Campus, Bethesda MD

New Ways to Skin a Cat — **October 15, 2003**
Presentation, PhysioGenix, Wauwatosa, WI

Discovery Channel Unsolved History Episode 23, Salem Witch Trials: Stability of ergot alkaloids under conditions of extreme heat — **October 22, 2003**

Discovery Channel Unsolved History Episode 21, Death of Marilyn Monroe: Pharmacokinetics of pentobarbital absorption — **October 1, 2003**

Another Way To Skin A Cat(hinone) — **June 15, 2003**
Presentation, Dept. of Pharmaceutical Sciences
University of Wisconsin School of Pharmacy, Madison, WI

Novel Monoaminergic Agents — **October 15, 2002**
Presentation, Dept. of Cellular and Molecular Pharmacology
Chicago Medical School, Finch University of Health Sciences, North Chicago, IL

Novel Monoaminergic Agents — **March 8, 2002**
Presentation, Dept. of Chemistry
East Carolina University, Greenville, NC

Novel Monoaminergic Agents — **February 21, 2002**
Presentation, Dept. of Physiology
East Carolina University, Greenville, NC

Probing Monoamine Transporters with Aminopropiophenones — **October 11,, 2000**
Presentation, Dept. of Physiology
East Carolina University, Greenville, NC

Teaching Skills for the Medical School Educator — **May 15, 2000**
Brody School of Medicine
East Carolina University, Greenville, NC

Mapping the Serotonin Reuptake Transporter — **July 16, 1999**
Presentation, Dept. of Medicinal Chemistry and Dept. of Pharmacology and Toxicology
Virginia Commonwealth University, Richmond, VA

Indan Analogues of Fenfluramine and Norfenfluramine Have Reduced Neurotoxic Potential — **March 17, 1999**
Presentation, Dept. of Pharmacology
East Carolina University, Greenville, NC

Mapping the Serotonin Reuptake Transporter — **March 8, 1999**
Presentation, Dept. of Biochemistry
East Carolina University, Greenville, NC

National Center of Leadership in Academic Medicine Personal Mentoring Program — **1999-2000**
Protégé, Brody School of Medicine
East Carolina University, Greenville, NC

Drugs of the Rainforest: A Pharmacological Sampler **Octobeer 18, 1995**
Presentation, The Rainforest Pharmacy
Massachusetts College of Pharmacy, Boston, MA

Nerve Gases: Mechanisms of Toxicity, Physiological Effects, and Antidotes **October 15, 1991**
Presentation, Pre-Medical Student Association
University of Wisconsin Medical School, Madison, WI

Drug Education at the College Level **February 2-3, 1991**
Panel Member, The Bridge Conference
Stanford University, Palo Alto, CA

PATENTS

Filtration agents and methods of use thereof. US patent number: US 20120167903 A1

PROFESSIONAL AFFILIATIONS

American Chemical Society (Division of Medicinal Chemistry)

American Society for Pharmacology and Experimental Therapeutics (Division for Neuropharmacology)

Multidisciplinary Association for Psychedelic Studies

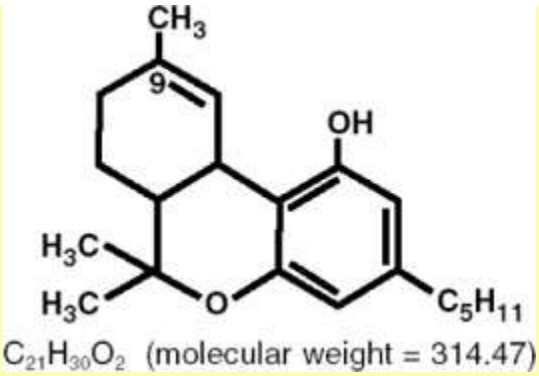
Society for Neuroscience (Division for Neuropharmacology and Neurochemistry)

MARINOL®
(dronabinol) Capsules

Rx Only
CIII

DESCRIPTION

Dronabinol is a cannabinoid designated chemically as (6*aR-trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol. Dronabinol has the following empirical and structural formulas:



$C_{21}H_{30}O_2$ (molecular weight = 314.47)

Dronabinol, the active ingredient in MARINOL® (dronabinol) Capsules, is synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a naturally occurring component of *Cannabis sativa L.* (Marijuana).

Dronabinol is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Dronabinol is insoluble in water and is formulated in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7.

Capsules for oral administration: MARINOL Capsules is supplied as round, soft gelatin capsules containing either 2.5 mg, 5 mg, or 10 mg dronabinol. Each MARINOL Capsule strength is formulated with the following inactive ingredients: 2.5 mg capsule contains gelatin, glycerin, sesame oil, and titanium dioxide; 5 mg capsule contains iron oxide red and iron oxide black, gelatin, glycerin, sesame oil, and titanium dioxide; 10 mg capsule contains iron oxide red and iron oxide yellow, gelatin, glycerin, sesame oil, and titanium dioxide.

CLINICAL PHARMACOLOGY

Dronabinol is an orally active cannabinoid which, like other cannabinoids, has complex effects on the central nervous system (CNS), including central sympathomimetic activity. Cannabinoid receptors have been discovered in neural tissues. These receptors may play a role in mediating the effects of dronabinol and other cannabinoids.

Pharmacodynamics

Dronabinol-induced sympathomimetic activity may result in tachycardia and/or conjunctival injection. Its effects on blood pressure are inconsistent, but occasional subjects have experienced orthostatic hypotension and/or syncope upon abrupt standing.

Dronabinol also demonstrates reversible effects on appetite, mood, cognition, memory, and perception. These phenomena appear to be dose-related, increasing in frequency with higher dosages, and subject to great interpatient variability.

After oral administration, dronabinol has an onset of action of approximately 0.5 to 1 hours and peak effect at 2 to 4 hours. Duration of action for psychoactive effects is 4 to 6 hours, but the appetite stimulant effect of dronabinol may continue for 24 hours or longer after administration.

Tachyphylaxis and tolerance develop to some of the pharmacologic effects of dronabinol and other cannabinoids with chronic use, suggesting an indirect effect on sympathetic neurons. In a study of the pharmacodynamics of chronic dronabinol exposure, healthy male volunteers (N = 12) received 210 mg/day dronabinol, administered orally in divided doses, for 16 days. An initial tachycardia induced by dronabinol was replaced successively by normal sinus rhythm and then bradycardia. A decrease in supine blood pressure, made worse by standing, was also observed initially. These volunteers developed tolerance to the cardiovascular and subjective adverse CNS effects of dronabinol within 12 days of treatment initiation.

Tachyphylaxis and tolerance do not, however, appear to develop to the appetite stimulant effect of MARINOL Capsules. In studies involving patients with Acquired Immune Deficiency Syndrome (AIDS), the appetite stimulant effect of MARINOL Capsules has been sustained for up to five months in clinical trials, at dosages ranging from 2.5 mg/day to 20 mg/day.

Pharmacokinetics

Absorption and Distribution: MARINOL Capsules is almost completely absorbed (90 to 95%) after single oral doses. Due to the combined effects of first pass hepatic metabolism and high lipid solubility, only 10 to 20% of the administered dose reaches the systemic circulation. Dronabinol has a large apparent volume of distribution, approximately 10 L/kg, because of its

lipid solubility. The plasma protein binding of dronabinol and its metabolites is approximately 97%.

The elimination phase of dronabinol can be described using a two compartment model with an initial (alpha) half-life of about 4 hours and a terminal (beta) half-life of 25 to 36 hours. Because of its large volume of distribution, dronabinol and its metabolites may be excreted at low levels for prolonged periods of time.

The pharmacokinetics of dronabinol after single doses (2.5, 5, and 10 mg) and multiple doses (2.5, 5, and 10 mg given twice a day; BID) have been studied in healthy women and men.

Summary of Multiple-Dose Pharmacokinetic Parameters of Dronabinol in Healthy Volunteers (n=34; 20-45 years) under Fasted Conditions

Mean (SD) PK Parameter Values			
BID Dose	**Cmax ng/mL**	**Median Tmax (range), hr**	**AUC(0-12) ng•hr/mL**
2.5 mg	1.32 (0.62)	1.00 (0.50-4.00)	2.88 (1.57)
5 mg	2.96 (1.81)	2.50 (0.50-4.00)	6.16 (1.85)
10 mg	7.88 (4.54)	1.50 (0.50-3.50)	15.2 (5.52)

A slight increase in dose proportionality on mean Cmax and AUC(0-12) of dronabinol was observed with increasing dose over the dose range studied.

Metabolism: Dronabinol undergoes extensive first-pass hepatic metabolism, primarily by microsomal hydroxylation, yielding both active and inactive metabolites. Dronabinol and its principal active metabolite, 11-OH-delta-9-THC, are present in approximately equal concentrations in plasma. Concentrations of both parent drug and metabolite peak at approximately 0.5 to 4 hours after oral dosing and decline over several days. Values for clearance average about 0.2 L/kg-hr, but are highly variable due to the complexity of cannabinoid distribution.

Elimination: Dronabinol and its biotransformation products are excreted in both feces and urine. Biliary excretion is the major route of elimination with about half of a radio-labeled oral dose being recovered from the feces within 72 hours as contrasted with 10 to 15% recovered from urine. Less than 5% of an oral dose is recovered unchanged in the feces.

Following single dose administration, low levels of dronabinol metabolites have been detected for more than 5 weeks in the urine and feces.

In a study of MARINOL Capsules involving AIDS patients, urinary cannabinoid/creatinine concentration ratios were studied bi-weekly over a six week period. The urinary

cannabinoid/creatinine ratio was closely correlated with dose. No increase in the cannabinoid/creatinine ratio was observed after the first two weeks of treatment, indicating that steady-state cannabinoid levels had been reached. This conclusion is consistent with predictions based on the observed terminal half-life of dronabinol.

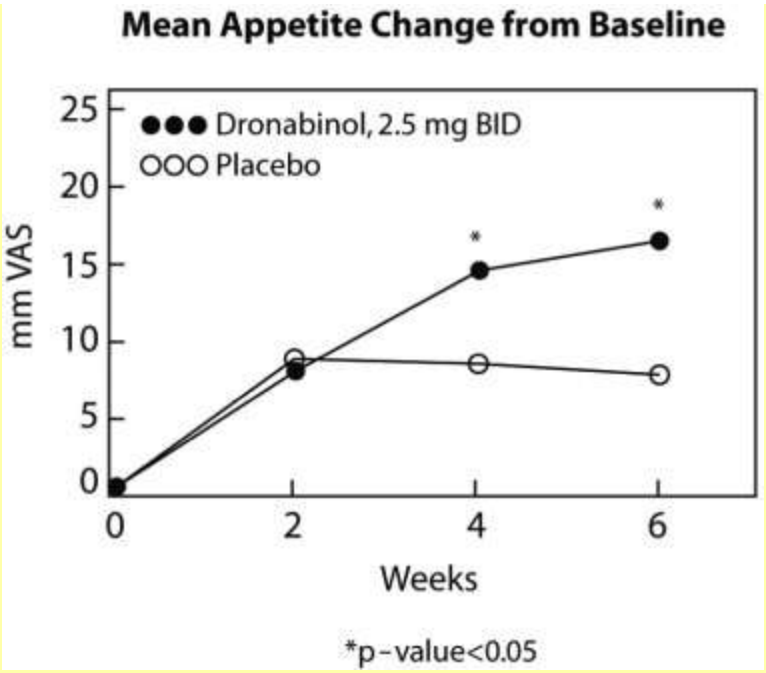
Special Populations: The pharmacokinetic profile of MARINOL Capsules has not been investigated in either pediatric or geriatric patients.

Clinical Trials

Appetite Stimulation: The appetite stimulant effect of MARINOL Capsules in the treatment of AIDS-related anorexia associated with weight loss was studied in a randomized, double-blind, placebo-controlled study involving 139 patients. The initial dosage of MARINOL Capsules in all patients was 5 mg/day, administered in doses of 2.5 mg one hour before lunch and one hour before supper. In pilot studies, early morning administration of MARINOL Capsules appeared to have been associated with an increased frequency of adverse experiences, as compared to dosing later in the day. The effect of MARINOL Capsules on appetite, weight, mood, and nausea was measured at scheduled intervals during the six-week treatment period. Side effects (feeling high, dizziness, confusion, somnolence) occurred in 13 of 72 patients (18%) at this dosage level and the dosage was reduced to 2.5 mg/day, administered as a single dose at supper or bedtime.

Of the 112 patients that completed at least 2 visits in the randomized, double-blind, placebo-controlled study, 99 patients had appetite data at 4-weeks (50 received MARINOL and 49 received placebo) and 91 patients had appetite data at 6-weeks (46 received MARINOL and 45 received placebo). A statistically significant difference between MARINOL Capsules and placebo was seen in appetite as measured by the visual analog scale at weeks 4 and 6 (see figure). Trends toward improved body weight and mood, and decreases in nausea were also seen.

After completing the 6-week study, patients were allowed to continue treatment with MARINOL Capsules in an open-label study, in which there was a sustained improvement in appetite.



Antiemetic: MARINOL Capsules treatment of chemotherapy-induced emesis was evaluated in 454 patients with cancer, who received a total of 750 courses of treatment of various malignancies. The antiemetic efficacy of MARINOL Capsules was greatest in patients receiving cytotoxic therapy with MOPP for Hodgkin's and non-Hodgkin's lymphomas. MARINOL Capsules dosages ranged from 2.5 mg/day to 40 mg/day, administered in equally divided doses every four to six hours (four times daily). As indicated in the following table, escalating the MARINOL Capsules dose above 7 mg/m^2 increased the frequency of adverse experiences, with no additional antiemetic benefit.

MARINOL Capsules Dose: Response Frequency and Adverse Experiences*(N = 750 treatment courses)

MARINOL Capsules Dose	**Response Frequency (%)**			**Adverse Events Frequency (%)**		
	Complete	Partial	Poor	None	Nondysphoric	Dysphoric
<7 mg/m^2	36	32	32	23	65	12
>7 mg/m^2	33	31	36	13	58	28

*Nondysphoric events consisted of drowsiness, tachycardia, etc.

Combination antiemetic therapy with MARINOL Capsules and a phenothiazine (prochlorperazine) may result in synergistic or additive antiemetic effects and attenuate the toxicities associated with each of the agents.

INDIVIDUALIZATION OF DOSAGES

The pharmacologic effects of MARINOL Capsules are dose-related and subject to considerable interpatient variability. Therefore, dosage individualization is critical in achieving the maximum benefit of MARINOL Capsules treatment.

Appetite Stimulation: In the clinical trials, the majority of patients were treated with 5 mg/day MARINOL Capsules, although the dosages ranged from 2.5 to 20 mg/day. For an adult:

1. Begin with 2.5 mg before lunch and 2.5 mg before supper. If CNS symptoms (feeling high, dizziness, confusion, somnolence) do occur, they usually resolve in 1 to 3 days with continued dosage.
2. If CNS symptoms are severe or persistent, reduce the dose to 2.5 mg before supper. If symptoms continue to be a problem, taking the single dose in the evening or at bedtime may reduce their severity.
3. When adverse effects are absent or minimal and further therapeutic effect is desired, increase the dose to 2.5 mg before lunch and 5 mg before supper or 5 and 5 mg. Although most patients respond to 2.5 mg twice daily, 10 mg twice daily has been tolerated in about half of the patients in appetite stimulation studies.

The pharmacologic effects of MARINOL Capsules are reversible upon treatment cessation.

Antiemetic: Most patients respond to 5 mg three or four times daily. Dosage may be escalated during a chemotherapy cycle or at subsequent cycles, based upon initial results. Therapy should be initiated at the lowest recommended dosage and titrated to clinical response. Administration of MARINOL Capsules with phenothiazines, such as prochlorperazine, has resulted in improved efficacy as compared to either drug alone, without additional toxicity.

Pediatrics: MARINOL Capsules is not recommended for AIDS-related anorexia in pediatric patients because it has not been studied in this population. The pediatric dosage for the treatment of chemotherapy-induced emesis is the same as in adults. Caution is recommended in prescribing MARINOL Capsules for children because of the psychoactive effects.

Geriatrics: Caution is advised in prescribing MARINOL Capsules in elderly patients because they may be more sensitive to the neurological, psychoactive and postural hypotensive effects of the drug. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (See PRECAUTIONS.)

MARINOL Capsules should be used with caution when administered to elderly patients with dementia, who are at increased risk for falls as a result of their underlying disease state which may be exacerbated by the central nervous system effects of somnolence and dizziness associated with MARINOL Capsules. These patients should be monitored closely and placed on fall precautions prior to initiating MARINOL therapy. In antiemetic studies, no difference in efficacy was apparent in patients >55 years old.

INDICATIONS AND USAGE

MARINOL Capsules is indicated for the treatment of:

1. anorexia associated with weight loss in patients with AIDS; and
2. nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

CONTRAINDICATIONS

MARINOL Capsules is contraindicated in any patient who has a known sensitivity to MARINOL Capsules or any of its ingredients. It contains cannabinoid and sesame oil and should never be used by patients allergic to these substances.

WARNINGS

Patients receiving treatment with MARINOL Capsules should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely.

PRECAUTIONS

General: The risk/benefit ratio of MARINOL Capsules use should be carefully evaluated in patients with the following medical conditions because of individual variation in response and tolerance to the effects of MARINOL Capsules.

Seizure and seizure-like activity have been reported in patients receiving MARINOL Capsules during marketed use of the drug and in clinical trials. (See **ADVERSE REACTIONS** and **OVERDOSAGE.**) MARINOL Capsules should be used with caution in patients with a history of seizure disorder because MARINOL Capsules may lower the seizure threshold. A causal relationship between MARINOL Capsules and these events has not been established. MARINOL Capsules should be discontinued immediately in patients who develop seizures and medical attention should be sought immediately.

MARINOL Capsules should be used with caution in patients with cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia. (See **CLINICAL PHARMACOLOGY.**)

MARINOL Capsules should be used with caution in patients with a history of substance abuse, including alcohol abuse or dependence, because they may be more prone to abuse MARINOL Capsules as well. Multiple substance abuse is common and marijuana, which contains the same active compound, is a frequently abused substance.

MARINOL Capsules should be used with caution and careful psychiatric monitoring in patients with mania, depression, or schizophrenia because MARINOL Capsules may exacerbate these illnesses.

MARINOL Capsules should be used with caution in patients receiving concomitant therapy with sedatives, hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS effects.

MARINOL Capsules should be used with caution in elderly patients because they may be more sensitive to the neurological, psychoactive, and postural hypotensive effects of the drug.(See **INDIVIDUALIZATION OF DOSAGES.**)

MARINOL Capsules should be used with caution in pregnant patients, nursing mothers, or pediatric patients because it has not been studied in these patient populations.

Information for Patients: Patients receiving treatment with MARINOL Capsules should be alerted to the potential for additive central nervous system depression if MARINOL Capsules is used concomitantly with alcohol or other CNS depressants such as benzodiazepines and barbiturates.

Patients receiving treatment with MARINOL Capsules should be specifically warned not to drive, operate machinery, or engage in any hazardous activity until it is established that they are able to tolerate the drug and to perform such tasks safely.

Patients using MARINOL Capsules should be advised of possible changes in mood and other adverse behavioral effects of the drug so as to avoid panic in the event of such manifestations. Patients should remain under the supervision of a responsible adult during initial use of MARINOL Capsules and following dosage adjustments.

Drug Interactions: In studies involving patients with AIDS and/or cancer, MARINOL Capsules has been co-administered with a variety of medications (e.g., cytotoxic agents, anti-infective

agents, sedatives, or opioid analgesics) without resulting in any clinically significant drug/drug interactions. Although no drug/drug interactions were discovered during the clinical trials of MARINOL Capsules, cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. Dronabinol is highly protein bound to plasma proteins, and therefore, might displace other protein-bound drugs. Although this displacement has not been confirmed *in vivo*, practitioners should monitor patients for a change in dosage requirements when administering dronabinol to patients receiving other highly protein-bound drugs. Published reports of drug/drug interactions involving cannabinoids are summarized in the following table.

CONCOMITANT DRUG	CLINICAL EFFECT(S)
Amphetamines, cocaine, other sympathomimetic agents	Additive hypertension, tachycardia, possibly cardiotoxicity
Atropine, scopolamine, antihistamines, other anticholinergic agents	Additive or super-additive tachycardia, drowsiness
Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants	Additive tachycardia, hypertension, drowsiness
Barbiturates, benzodiazepines, ethanol, lithium, opioids, buspirone, antihistamines, muscle relaxants, other CNS depressants	Additive drowsiness and CNS depression
Disulfiram	A reversible hypomanic reaction was reported in a 28 y/o man who smoked marijuana; confirmed by dechallenge and rechallenge
Fluoxetine	A 21 y/o female with depression and bulimia receiving 20 mg/day fluoxetine X 4 wks became hypomanic after smoking marijuana; symptoms resolved after 4 days
Antipyrine, barbiturates	Decreased clearance of these agents, presumably via competitive inhibition of metabolism
Theophylline	Increased theophylline metabolism reported with smoking of marijuana; effect similar to that following smoking tobacco

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies in mice and rats have been conducted under the US National Toxicology Program (NTP). In the 2-year carcinogenicity study in rats, there was no evidence of carcinogenicity at doses up to 50 mg/kg/day, about 20 times the maximum recommended human dose on a body surface area basis. In the 2-year carcinogenicity study in mice, treatment with dronabinol at 125 mg/kg/day, about 25 times the maximum recommended human dose on a body surface area basis, produced thyroid follicular cell adenoma in both male and female mice but not at 250 or 500 mg/kg/day.

Dronabinol was not genotoxic in the Ames tests, the *in vitro* chromosomal aberration test in Chinese hamster ovary cells, and the *in vivo* mouse micronucleus test. It, however, produced a weak positive response in a sister chromatid exchange test in Chinese hamster ovary cells.

In a long-term study (77 days) in rats, oral administration of dronabinol at doses of 30 to 150 mg/m^2, equivalent to 0.3 to 1.5 times maximum recommended human dose (MRHD) of 90

mg/m^2/day in cancer patients or 2 to 10 times MRHD of 15 mg/m^2/day in AIDS patients, reduced ventral prostate, seminal vesicle and epididymal weights and caused a decrease in seminal fluid volume. Decreases in spermatogenesis, number of developing germ cells, and number of Leydig cells in the testis were also observed. However, sperm count, mating success and testosterone levels were not affected. The significance of these animal findings in humans is not known.

Pregnancy: Pregnancy Category C. Reproduction studies with dronabinol have been performed in mice at 15 to 450 mg/m^2, equivalent to 0.2 to 5 times maximum recommended human dose (MRHD) of 90 mg/m^2/day in cancer patients or 1 to 30 times MRHD of 15 mg/m^2/day in AIDS patients, and in rats at 74 to 295 mg/m^2 (equivalent to 0.8 to 3 times MRHD of 90 mg/m^2 in cancer patients or 5 to 20 times MRHD of 15 mg/m^2/day in AIDS patients). These studies have revealed no evidence of teratogenicity due to dronabinol. At these dosages in mice and rats, dronabinol decreased maternal weight gain and number of viable pups and increased fetal mortality and early resorptions. Such effects were dose dependent and less apparent at lower doses which produced less maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Dronabinol should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Use of MARINOL Capsules is not recommended in nursing mothers since, in addition to the secretion of HIV virus in breast milk, dronabinol is concentrated in and secreted in human breast milk and is absorbed by the nursing baby.

Geriatric Use: Clinical studies of MARINOL Capsules in AIDS and cancer patients did not include the sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of falls, decreased hepatic, renal, or cardiac function, increased sensitivity to psychoactive effects and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Adverse experiences information summarized in the tables below was derived from well-controlled clinical trials conducted in the US and US territories involving 474 patients exposed to MARINOL Capsules. Studies of AIDS-related weight loss included 157 patients receiving dronabinol at a dose of 2.5 mg twice daily and 67 receiving placebo. Studies of different durations were combined by considering the first occurrence of events during the first 28 days.

Studies of nausea and vomiting related to cancer chemotherapy included 317 patients receiving dronabinol and 68 receiving placebo.

A cannabinoid dose-related "high" (easy laughing, elation and heightened awareness) has been reported by patients receiving MARINOL Capsules in both the antiemetic (24%) and the lower dose appetite stimulant clinical trials (8%). (See **Clinical Trials.**)

The most frequently reported adverse experiences in patients with AIDS during placebo-controlled clinical trials involved the CNS and were reported by 33% of patients receiving MARINOL Capsules. About 25% of patients reported a minor CNS adverse event during the first 2 weeks and about 4% reported such an event each week for the next 6 weeks thereafter.

PROBABLY CAUSALLY RELATED: Incidence greater than 1%.

Rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N=317). Rates were generally higher in the anti-emetic use (given in parentheses).

Body as a whole: Asthenia. *Cardiovascular:* Palpitations, tachycardia, vasodilation/facial flush. *Digestive:* Abdominal pain*, nausea*, vomiting*. *Nervous system:* (Amnesia), anxiety/nervousness, (ataxia), confusion, depersonalization, dizziness*, euphoria*, (hallucination), paranoid reaction*, somnolence*, thinking abnormal*.
*Incidence of events 3% to 10%

PROBABLY CAUSALLY RELATED: Incidence less than 1%.

Event rates derived from clinical trials in AIDS-related anorexia (N=157) and chemotherapy-related nausea (N=317).

Cardiovascular: Conjunctivitis*, hypotension*. *Digestive:* Diarrhea*, fecal incontinence. *Musculoskeletal:* Myalgias. *Nervous system:* Depression, nightmares, speech difficulties, tinnitus. *Skin and Appendages:* Flushing*. *Special senses:* Vision difficulties.
*Incidence of events 0.3% to 1%

CAUSAL RELATIONSHIP UNKNOWN: Incidence less than 1%.

The clinical significance of the association of these events with MARINOL Capsules treatment is unknown, but they are reported as alerting information for the clinician.

Body as a whole: Chills, headache, malaise. *Digestive:* Anorexia, hepatic enzyme elevation. *Respiratory:* Cough, rhinitis, sinusitis. *Skin and Appendages:* Sweating.

Postmarketing Experience

Seizure and seizure-like activity have been reported in patients receiving MARINOL Capsules during marketed use of the drug and in clinical trials. (See **PRECAUTIONS and OVERDOSAGE.**) **Reports of fatigue have also been received.** A causal relationship between MARINOL Capsules and these events has not been established.

DRUG ABUSE AND DEPENDENCE

MARINOL Capsules is one of the psychoactive compounds present in cannabis, and is abusable and controlled [Schedule III (CIII)] under the Controlled Substances Act. Both psychological and physiological dependence have been noted in healthy individuals receiving dronabinol, but addiction is uncommon and has only been seen after prolonged high dose administration.

Chronic abuse of cannabis has been associated with decrements in motivation, cognition, judgement, and perception. The etiology of these impairments is unknown, but may be associated with the complex process of addiction rather than an isolated effect of the drug. No such decrements in psychological, social or neurological status have been associated with the administration of MARINOL Capsules for therapeutic purposes.

In an open-label study in patients with AIDS who received MARINOL Capsules for up to five months, no abuse, diversion or systematic change in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse.

An abstinence syndrome has been reported after the abrupt discontinuation of dronabinol in volunteers receiving dosages of 210 mg/day for 12 to 16 consecutive days. Within 12 hours after discontinuation, these volunteers manifested symptoms such as irritability, insomnia, and restlessness. By approximately 24 hours post-dronabinol discontinuation, withdrawal symptoms intensified to include “hot flashes”, sweating, rhinorrhea, loose stools, hiccoughs and anorexia.

These withdrawal symptoms gradually dissipated over the next 48 hours. Electroencephalographic changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt dechallenge. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high dosages of dronabinol.

OVERDOSAGE

Signs and symptoms following MILD MARINOL Capsules intoxication include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth and tachycardia; following MODERATE intoxication include memory impairment,

depersonalization, mood alteration, urinary retention, and reduced bowel motility; and following SEVERE intoxication include decreased motor coordination, lethargy, slurred speech, and postural hypotension. Apprehensive patients may experience panic reactions and seizures may occur in patients with existing seizure disorders.

The estimated lethal human dose of intravenous dronabinol is 30 mg/kg (2100 mg/ 70 kg). Significant CNS symptoms in antiemetic studies followed oral doses of 0.4 mg/kg (28 mg/70 kg) of MARINOL Capsules.

Management: A potentially serious oral ingestion, if recent, should be managed with gut decontamination. In unconscious patients with a secure airway, instill activated charcoal (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal. Patients experiencing depressive, hallucinatory or psychotic reactions should be placed in a quiet area and offered reassurance. Benzodiazepines (5 to 10 mg diazepam *po*) may be used for treatment of extreme agitation. Hypotension usually responds to Trendelenburg position and IV fluids. Pressors are rarely required.

DOSAGE AND ADMINISTRATION

Appetite Stimulation: Initially, 2.5 mg MARINOL Capsules should be administered orally twice daily (b.i.d.), before lunch and supper. For patients unable to tolerate this 5 mg/day dosage of MARINOL Capsules, the dosage can be reduced to 2.5 mg/day, administered as a single dose in the evening or at bedtime. If clinically indicated and in the absence of significant adverse effects, the dosage may be gradually increased to a maximum of 20 mg/day MARINOL Capsules, administered in divided oral doses. Caution should be exercised in escalating the dosage of MARINOL Capsules because of the increased frequency of dose-related adverse experiences at higher dosages. (See **PRECAUTIONS.**)

Antiemetic: MARINOL Capsules is best administered at an initial dose of 5 mg/m^2, given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy is given, for a total of 4 to 6 doses/day. Should the 5 mg/m^2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose. Caution should be exercised in dose escalation, however, as the incidence of disturbing psychiatric symptoms increases significantly at maximum dose. (See **PRECAUTIONS.**)

Storage Conditions

MARINOL Capsules should be packaged in a well-closed container and stored in a cool environment between 8° and 15°C (46° and 59°F) and alternatively could be stored in a refrigerator. Protect from freezing.

HOW SUPPLIED

MARINOL Capsules (dronabinol solution in sesame oil in soft gelatin capsules)

2.5 mg white capsules (Identified UM).
NDC 0051-0021-21 (Bottle of 60 capsules).

5 mg dark brown capsules (Identified UM).
NDC 0051-0022-21 (Bottle of 60 capsules).

10 mg orange capsules (Identified UM).
NDC 0051-0023-21 (Bottle of 60 capsules).

Manufactured by:
Banner Pharmacaps, Inc.
High Point, NC 27265

For:
AbbVie Inc.
North Chicago, IL 60064, U.S.A.

PATIENT INFORMATION

MARINOL® (dronabinol)
Capsules
2.5 mg, 5 mg, 10 mg
for use in the loss of appetite
associated with weight loss
in patients with AIDS.

IMPORTANT

YOUR DOCTOR HAS PRESCRIBED THIS DRUG FOR YOUR USE ONLY. DO NOT LET ANYONE ELSE USE IT.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN AND PETS. If a child puts a capsule in his or her mouth or swallows MARINOL® Capsules, take the medicine away from the child and contact a poison control center immediately, or contact a doctor immediately.

Do not drive a car or operate machinery until you know how MARINOL Capsules affects you. While taking MARINOL Capsules, do not drink alcohol, smoke marijuana, or take other drugs that have an effect on the central nervous system (such as sedatives or hypnotics). Unless advised by your doctor, do not use MARINOL Capsules if you are pregnant or nursing.

INTRODUCTION

This leaflet provides a summary of information about MARINOL Capsules. Please read it and keep it with your medicines in case you need to look at it again. Ask your doctor, nurse, or pharmacist if you have any questions.

MARINOL Capsules contains man-made dronabinol (THC). Dronabinol also occurs naturally, and has been extracted from *Cannabis sativa L*. (marijuana).

PRECAUTIONS

Be sure to tell your doctor if you:

- have or had heart disease
- have or had cardiac disorders because of occasional hypotension, possible hypertension, syncope, or tachycardia
- have current or a history of drug abuse
- have current or a history of alcohol abuse
- have or had mental health problems (mania, depression, schizophrenia)
- have a history of seizure disorder and/or seizure-like activity
- have allergies to drugs
- are pregnant or nursing, or become pregnant

If you become pregnant while taking MARINOL Capsules, stop using it until you have talked to your doctor.

MARINOL Capsules should be used with caution in children because it has not been studied in children.

MARINOL Capsules should be used with caution in elderly patients because they may be more sensitive to the neurological, psychoactive, and postural hypotensive effects of the drug.

MARINOL Capsules can dangerously interact with alcohol and with other drugs that have an effect on the central nervous system (such as Valium, Librium, Xanax, Seconal, Nembutal, or Phenobarbital).

Do not drive or operate machinery until you are sure how MARINOL Capsules affects you and you are able to perform safely.

You may experience changes in mood or have other effects when first taking MARINOL Capsules. Be sure that there is a responsible person nearby when you first take MARINOL Capsules or when there is an adjustment in your dose.

Tell your doctor if you are taking any other prescription or nonprescription medicines.

Do not smoke marijuana while using MARINOL Capsules. This can cause an overdose.

INFORMATION ABOUT USING MARINOL CAPSULES

Introduction

Eating a nutritionally balanced diet is fundamental for all stages of life. For persons living with Human Immunodeficiency Virus (HIV); it's especially important to ensure an adequate diet to maintain an ideal weight and good nutritional status. There is some indication that optimal nutrition can help maintain the integrity of the immune system, and an adequate diet will allow you to better withstand the diseases associated with an AIDS diagnosis.

Many conditions, frequently interrelated, may cause a loss of appetite. Chewing and swallowing may become difficult or painful, due to inflammation or sores in your mouth and throat.

You may experience intermittent diarrhea or overall physical discomfort associated with AIDS. Sometimes, shopping for food and preparing adequate meals may drain your energy and desire to eat. Mental depression also may result in a loss of your appetite, or you simply may grow increasingly frustrated with repeated eating problems.

A loss of appetite may occur at various times during illness associated with HIV infection. It often leads to the selection of an inadequate diet. Because a poor nutrient intake can result in weight loss and malnutrition, it's important to learn to recognize and handle a temporary loss of your appetite.

Your doctor may prescribe an appetite stimulant such as MARINOL Capsules. MARINOL Capsules should be taken exactly as directed by your doctor, and indicated on the prescription label. You will most likely start therapy by taking one white capsule (2.5 mg) of MARINOL Capsules twice daily, before lunch and supper. Your doctor may adjust your MARINOL Capsules dosage if needed to maximize its effect or to decrease any side effects.

If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double your dose. MARINOL Capsules must be swallowed whole to work effectively. Do not crush or chew the capsules.

It is important not to take sedatives, hypnotics, other mind altering substances, or alcohol, while taking MARINOL Capsules without notifying your health care givers (physician, pharmacists and nurses). Do not drive or attempt other activities requiring full alertness while taking MARINOL Capsules. Your doctor will advise when you may resume these activities.

Your doctor and pharmacist should be made aware of any other prescription medications or over-the-counter products you may be taking, as they could affect the way you respond to MARINOL Capsules.

Remember to keep this and all other medication out of the reach of children.

Increasing your appetite is only the first step in improving your nutritional status. How, what, and when you eat are also very important.

How to Eat

The purpose of consuming an adequate diet, even at times when you don't feel like eating, is to maintain an ideal weight and good nutritional status. Key to an adequate diet for HIV-infected individuals are foods dense in calories and nutrients. In other words, when you find it difficult to eat, make the most of what you do consume by selecting foods that provide many calories or nutrients in each mouthful.

Try some of the following ideas to boost your food intake. Keep in mind the foods you previously may have limited in your diet, especially those higher in fat, now can provide a significant source of calories. Enjoy an ice cream sundae frequently.

Cool or cold foods can dull pain from mouth and throat sores; popsicles may even numb your mouth prior to eating a larger meal. The cooler temperatures also diminish the aroma of unappetizing food.

Blend one cup of nonfat dry milk powder with one quart of whole milk. Refrigerate and use "double strength" milk for all traditional uses (puddings, cereal, shakes, soups).

Foods with a softer consistency, such as applesauce, may aid swallowing. Creamed sauces or gravies also moisten food to encourage swallowing.

Creating an appetizing meal involves more than just food. Try to eat in a pleasant atmosphere – sit in a comfortable chair, use a tablecloth and china, invite a friend to share your meal.

What to Eat

Planning ahead is one of the most effective ways to deal with a loss of appetite. Stock up on staple foods, particularly those high in calories and protein, so they're available when you need them. Include favorite foods on your shopping list. Also consider these protein and nutrient dense foods:

- Nonfat dry milk powder
- Powdered breakfast drinks
- Peanut butter and jelly
- Pudding cups
- "Trail mix" (dried fruit, nuts, cereals)
- Creamed soups
- Canned (or frozen) fruit in heavy syrup
- Canned tuna, chicken or other sandwich spreads
- Boxed macaroni and cheese

In addition to staples, refrigerated and frozen foods contribute important nutrients to an adequate diet. Several key choices, high in protein and calories, are listed below:

- Yogurt
- Cheeses
- Cold cuts, beef and poultry
- Cottage cheese
- Ice cream and sherbet
- Popsicles or pudding pops

- Hard cooked eggs or pasteurized eggs*

*Raw or undercooked cracked eggs pose danger of *Salmonella*. The compromised immune function of persons with AIDS places them at greater than average risk from *Salmonella* infection.

Commercial food supplements are also available to boost your caloric and nutrient intake. Offered in a variety of flavors and textures, these products supply a concentrated source of calories and protein. You may want to ask your treatment provider for more information about supplements. You may also request a referral to a registered dietitian who can provide individualized dietary recommendations to you.

When to Eat

"Nutritious" meals can be eaten three times a day, but frequent, small snacks or meals can help you consume the calories and protein you need without feeling full from a large meal. Eat when you feel hungry, using modern technology, including your microwave, to quickly prepare a nutritious snack or meal.

Storage Instructions

The best place to store MARINOL Capsules is in a cool place (46-59°F; 8-15°C) or in the refrigerator. Be careful that the capsules don't freeze. Heat or moisture may cause your MARINOL Capsules to break down or stick together, so keep your medicine away from heat and direct light, and potentially damp places like in the bathroom or near the kitchen sink.

If You Are Taking Medicines

MARINOL Capsules use may change the effect of other medicines. It is important to tell your doctor about all the medicines you are taking including all non-prescription medication.

What to Watch For (Adverse Effects)

You should not smoke marijuana while using MARINOL Capsules. It is possible to get too much dronabinol (an overdose), especially if you use MARINOL Capsules and smoke marijuana at the same time. Signs of a mild overdose would include drowsiness, euphoria, heightened sensory awareness, altered time perception, red eyes, dry mouth and rapid heart rate (tachycardia). Moderate overdosage would produce memory problems, depersonalization, mood alteration, urinary retention, and constipation. Severe overdosage would lead to decreased motor coordination, lethargy, slurred speech, and dizziness when standing up too fast (postural hypotension).

An overdose might cause you to faint.

If You Have Problems in the First Few Days

When you first use MARINOL Capsules your body is more sensitive and you may experience dizziness, confusion, sleepiness, or a high feeling. These symptoms usually go away in 1 to 3 days with continued dosage. If these symptoms are troublesome or persist, notify your doctor at once. Your doctor may then reduce the dose to one capsule before supper, or later in the evening, or even at bedtime.

What to Do When Problems Occur

IF YOU NOTICE ANY WORRISOME SYMPTOMS OR PROBLEMS, STOP THE MARINOL CAPSULES AND CALL YOUR DOCTOR AT ONCE.

Manufactured by:
Banner Pharmacaps, Inc.
High Point, NC 27265

For:
AbbVie Inc.
North Chicago, IL 60064, U.S.A.

46628-01 February, 2013