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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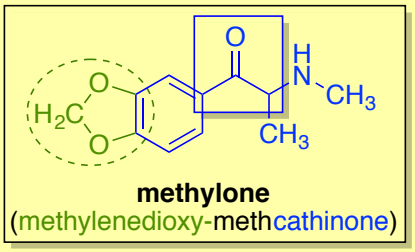
Tallahassee, FL 32306-4390, gdudley@chem.fsu.edu

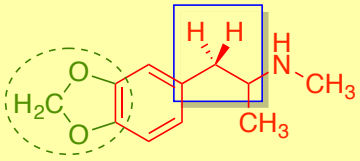
Overview

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.

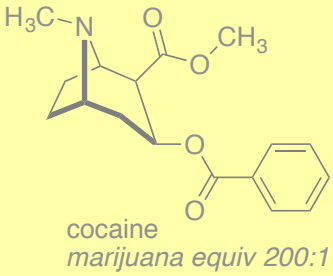
However, one can extrapolate from trends in how the Guidelines treat listed substances that are structurally and/or pharmacologically comparable to methylone to arrive at a reasonable marijuana equivalency treatment for methylone. For the reasons set forth herein, it would be hard scientifically to rationalize 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.



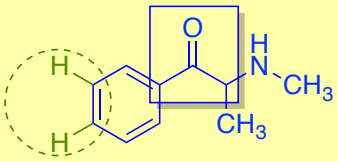
methylone
(methylenedioxy-methcathinone)



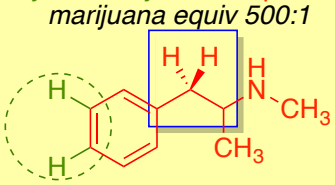
MDMA
(methylenedioxy-methamphetamine)
marijuana equiv 500:1



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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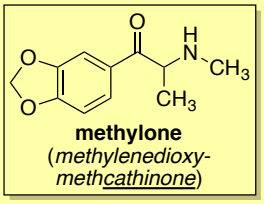
Executive Summary

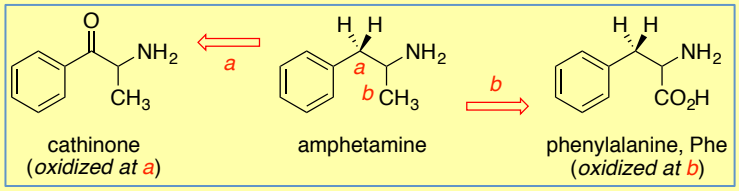


methylone
(*methylenedioxy-methcathinone*)

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.

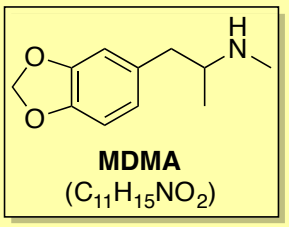
What is "*substantially similar*"? There is no scientifically accepted standard or definition of "*substantially similar*". Therefore, it can be difficult to interpret the definition of a Controlled Substance Analogue and Sentencing Guidelines scientifically; reasonable people might disagree on whether 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*.

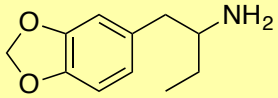
What is an *isomer*? Any reference in the Guidelines to a controlled substance includes all of its ***isomers***. However, the term "isomer" as applied is different from how it is used in chemistry. In chemistry, isomers are different structures having the same chemical formula (elemental composition). *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."*

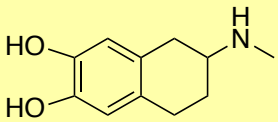
Three chemical isomers of $C_{11}H_{15}NO_2$ are illustrated below to exemplify the restrictions in place for which substances can be included among the controlled substances referenced in the Guidelines.



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.

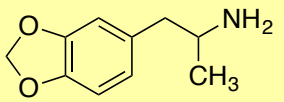
The definition of positional isomer reflects the importance of functional groups when considering chemical structures. One could argue that the first two structures are "substantially similar" (i.e., similar enough to be treated the same in law), but the third structure has different functional groups 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:

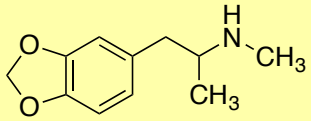
If structures that *are isomers* but do not share the same core structure and functional groups are not similar enough in chemical structure to be treated the same in law,
then compounds that *are not isomers* and do not share the same core structure and functional groups are also not similar enough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

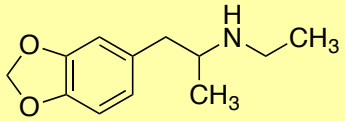
⟸ *(treated the same in the Sentencing Guidelines)* ⟹



methylenedioxy-amphetamine
(MDA)
marijuana equiv 500:1



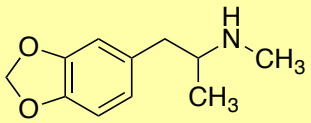
methylenedioxy-methamphetamine
(MDMA)
marijuana equiv 500:1



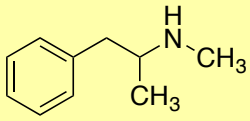
methylenedioxy-ethamphetamine
(MDEA)
marijuana equiv 500:1

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

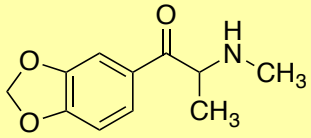


methamphetamine
marijuana equiv 20,000:1

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

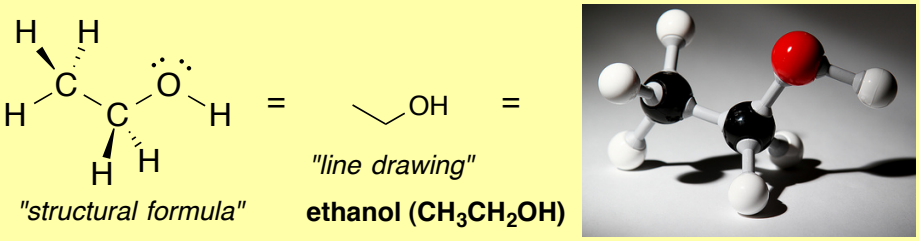
The Guidelines do *not* say to apply the marijuana equivalency of the most comparable substance to the unlisted substance (unless the unlisted substance is an isomer or analogue). It would not be logical to treat comparable substances as equivalent unless they are "substantially similar". As is noted 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

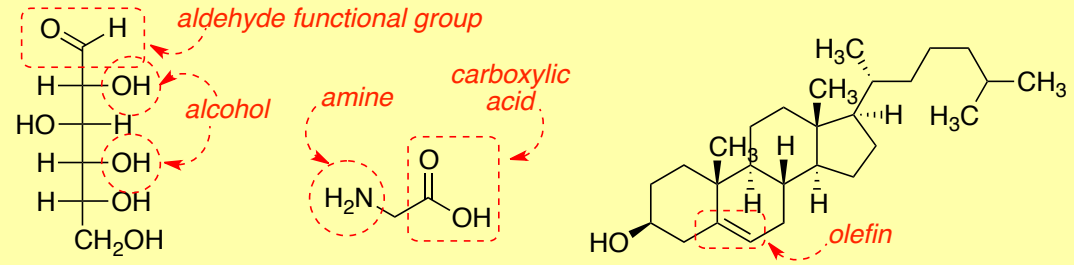
*"Whether the controlled substance not referenced in this guideline has a **chemical structure** that is substantially similar to a controlled substance referenced in this guideline."*

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.



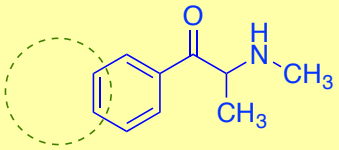
The chemical properties of the organic compound are based on the arrangement of functional groups in three-dimensional space, as well as the size, shape, and dynamics of the compound. Common functional groups include alcohols, olefins, amines, aldehydes, ketones, carboxylic acids, and halogens, with 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.



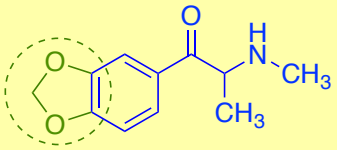
What is and is not "*substantially similar*"? As noted above, the term "*substantially similar*" is a legal term; it is not defined in the scientific literature. Indeed, *molecular similarity is impossible to define*.[4] Nonetheless, subjective similarity assessments are central to medicinal chemistry 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.

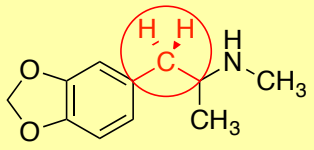


methcathinone
marijuana equiv 350:1

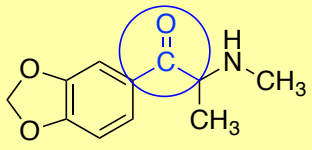


methylone
(methylenedioxy-methcathinone)

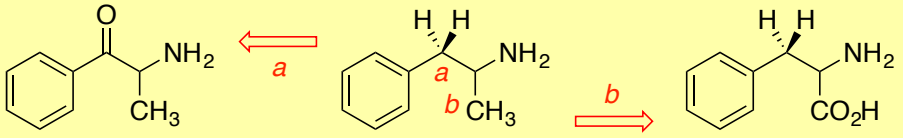
Methylone is NOT "substantially similar" to MDMA. Methylone is a cathinone, and MDMA is an amphetamine. The difference between a cathinone and an amphetamine is that *one carbon of cathinone is oxidized to its highest level relative to amphetamine*, resulting in the introduction of a ketone functional 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*)

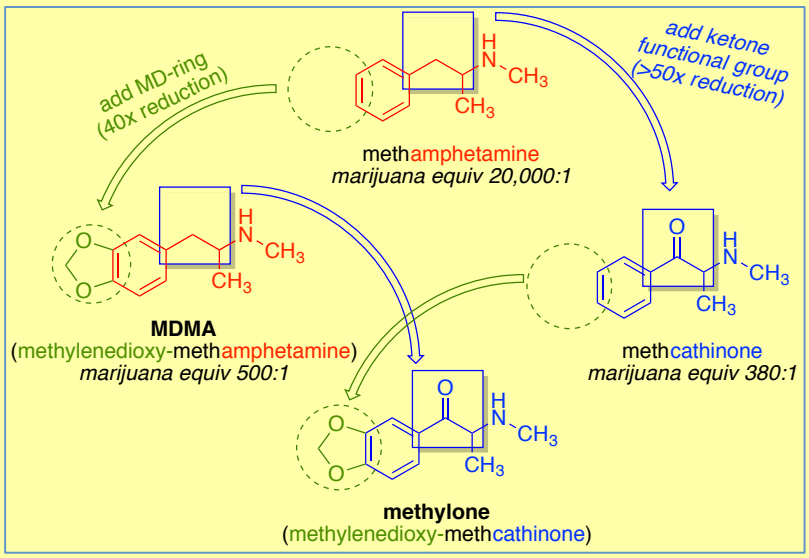
amphetamine

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).

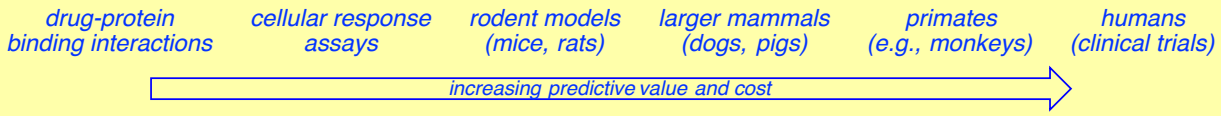
Part B: Effects on the Central Nervous System

"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.

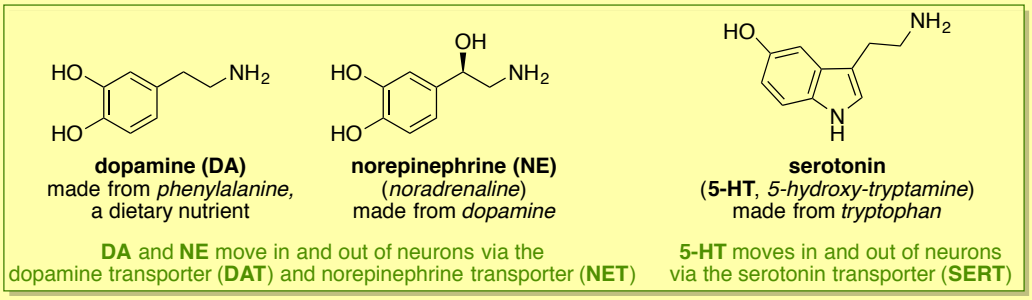


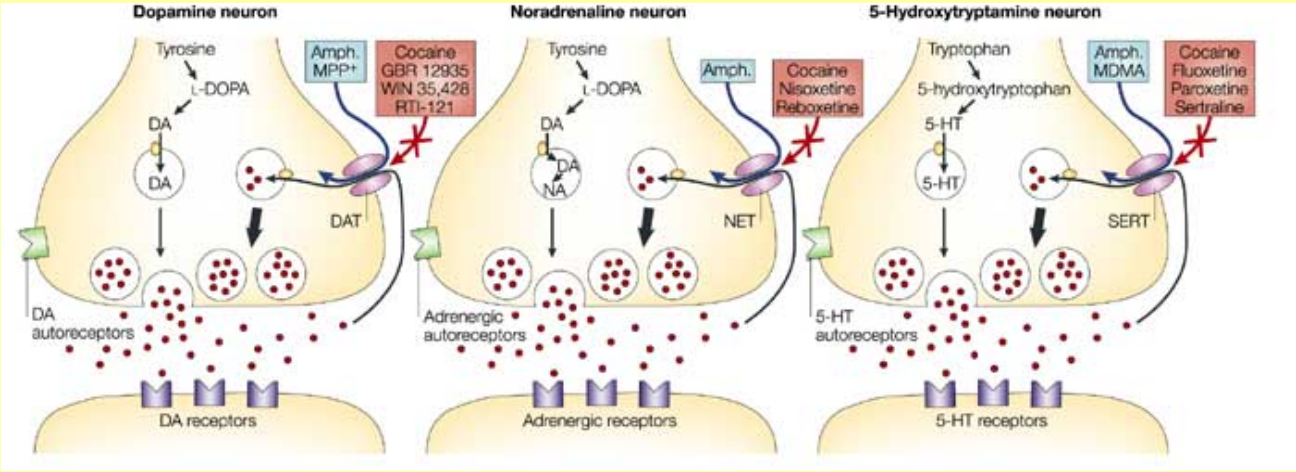
All of these types of pre-clinical studies provide important information that can be used to generate hypotheses as to how the drugs will perform in humans. Pharmaceutical researchers routinely use these studies to guide decisions on which drugs they will develop further toward the goal of putting a 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]





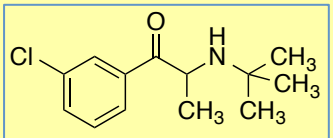
"FIGURE 1 | Schematic representation of dopamine, noradrenaline and 5-HT synaptic terminals. Monoamine transporters are localized to perisynaptic sites, where they are crucial for the termination of monoamine transmission and the maintenance of presynaptic monoamine storage. Several selective pharmacological 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.)

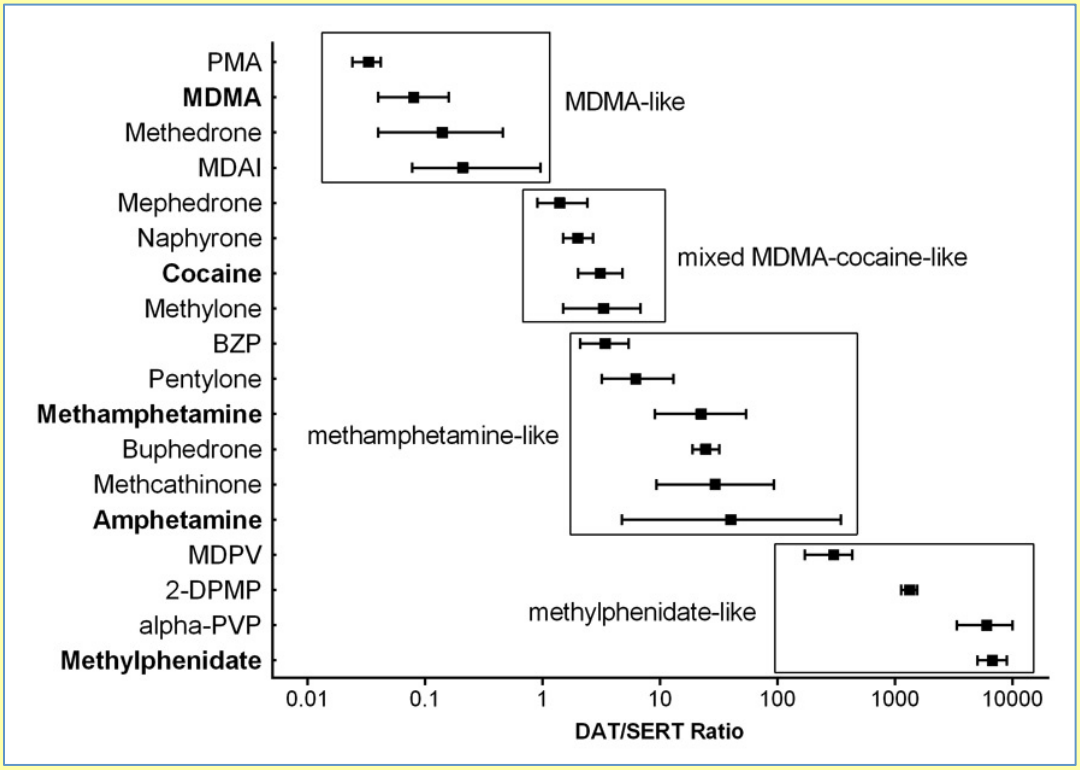
One well-studied synthetic cathinone is bupropion (Wellbutrin), which is prescribed for depression, smoking cessation, anxiety, and other indications related to neurochemical regulation. It primarily acts on serotonin transporters (SERT), with weaker impacts on DAT and NET in laboratory studies that 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*.

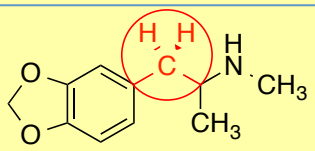
Summary of Part 3. Recent data from the Baumann lab at NIDA in rats demonstrate that: (a) there is good correlation between in vitro and in vivo experiments; (b) the immediate effects of methylone are qualitatively similar to but less potent than MDMA; and (c) repeated administration of methylone produced 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

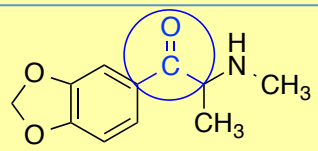
The illegal designer drug market has been described as an underground version of the pharmaceutical industry.[26] Whereas pharmaceutical companies aim to develop marketable therapeutics without infringing on competing patents, underground chemists aim to develop marketable drugs of abuse while staying 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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United States Department of Justice

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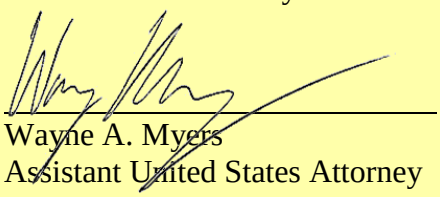
[3] Mr. Carlson, as part of his plea agreement, waived his right to appeal any sentence to a term of imprisonment of 188 months or less. Mr. Marshall, as part of his plea agreement, waived his right to appeal any sentence to a term of imprisonment of 121 months or less.

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

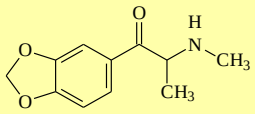
Introduction

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.

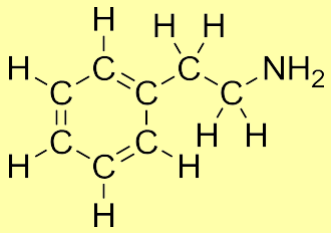
Substance at issue: 1-(1,3-benzodioxol-5-yl)-2-(methylamino) propan-1-one; 3,4-methylenedioxymethcathinone

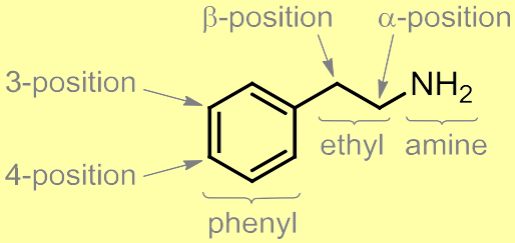
Alternate name: Methylone

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:

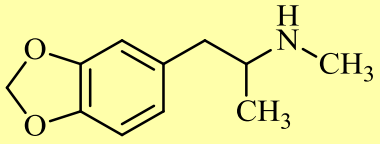
1. The core chemical structure of methylone and MDMA is phenethylamine. The figures below depict the chemical structure of phenethylamine. The figure on the left is a representation with every carbon (C) and hydrogen (H) atom shown for illustrative purposes. The figure on the right uses the most commonly 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.



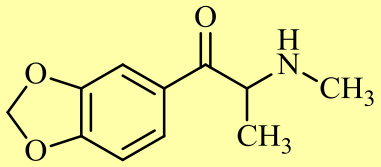


2. Methylone and MDMA share the same core chemical structure and are both substituted at the alpha (α)-position, on the phenyl ring, and on the nitrogen atom (N) of the phenethylamine core. Methylone is substituted with an oxygen atom (O) at the beta (β)-position, which is lacking in MDMA.

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

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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.

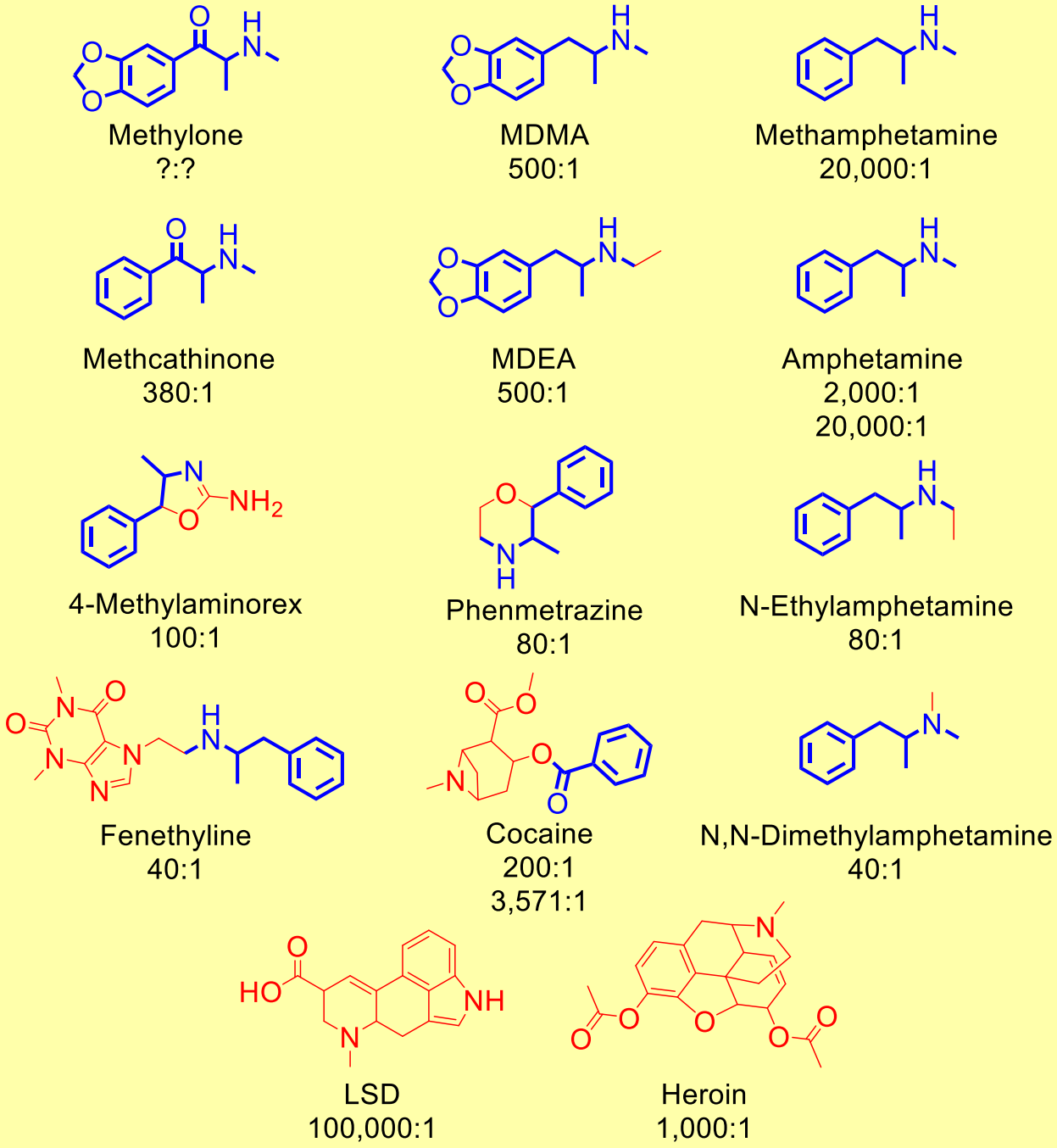

Figure 1: Chemical structures of methylone and related drugs from the Sentencing Guidelines. Structural features of each drug that are shared with methylone are shown in blue with thicker lines. Structural features that are not shared with methylone are shown in red with thinner lines. The drugs LSD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

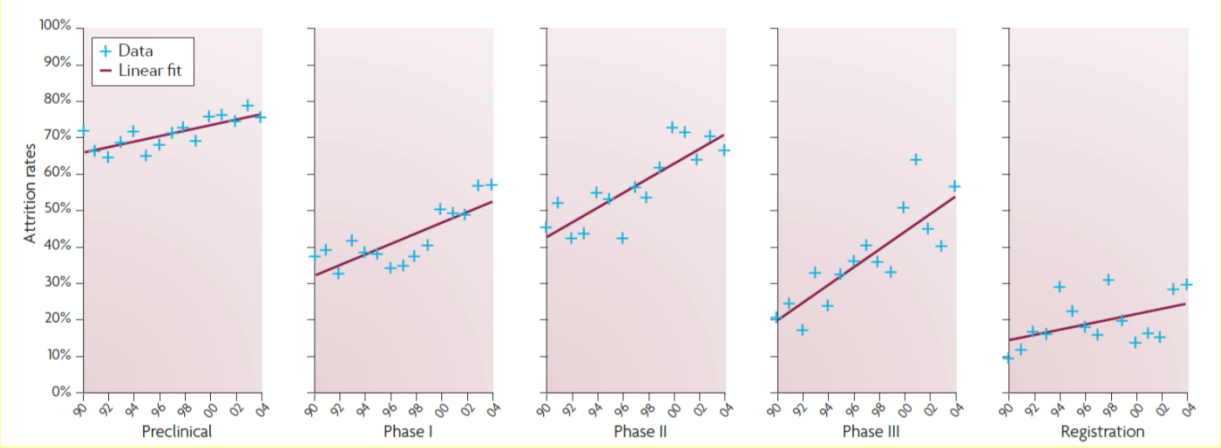

Figure 2. Drug Attrition Rates During Clinical Trials Following *in vitro* and Animal Studies from 1990 to 2004. Figure is reproduced from Pamollii *et al*, 2011[13].

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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