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Paul Grof, M.D., Chairman
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Dear Dr. Grof:

Your name has been given me, as a person who will be at the forthcoming WHO meetings, where consideration will be given to recommendations for the international scheduling of potentially hazardous drugs. The agenda includes a discussion of a drug MDMA (N,alpha-dimethyl-1,3-benzodioxole-5-ethaneamine), a material that is currently being appraised in a series of judicial hearings as to legal status within the United States. A major focal point of argument there has been its structural and pharmacological relationship to the known Schedule I drug MDA. I have conducted numerous studies on these two drugs and feel that I can validly compare them. Most of these studies have been published, and these writings are being called upon to support the arguments of both sides. I would like to share with you the findings that have led me to my present understanding.

Two specific questions are at hand that are needing answers, and that have been interpreted in misleading ways. Let me try to clarify these as best I can. One deals with a paraphrasing presented in subsection number 8.28 of the WHO document that quotes me as saying that MDMA has a hallucinogenic activity similar to mescaline. I have been told that this document was written by Drs. Wood and Schuster, and I am sending a copy of this letter to both. The second point specifically addresses the similarities and differences between MDMA and MDA. Let me take them in turn.

The WHO subsection number 8.28 gives comment in entries #3 entitled General Pharmacology, and in entries #13 entitled Abstracts and Bibliography. Let me take the citation before I take the quotation. Under #13, my 1982 citation (page 14, in Hoffmeister and Stille's PSYCHOTROPIC EFFECTS OF CENTRAL ACTING DRUGS) abstracts my comments on the potency of several substituted amphetamines. It states explicitly that "although most show a striking drop in potency, MDMA (the N-methyl homologue of MDA) retains full activity. This is correct, and I

am completely at peace with it. MDMA is indeed fully as potent as MDA. But here the context is one of potency, and is carefully restricted to a quantitative description of action. And yet, based only upon this quotation from my findings, the following paraphrase was entered into the text of this report, under #3:

Shulgin (1982) reports that MDMA has hallucinogenic activity similar to mescaline.

This is inaccurate. No mention was made at any point of mescaline and the cited quote suggests a qualitative comparison.

As to the second question, let me reprint a distillation that I wrote to Dr. George Greer a couple of days ago, that calls upon both published and unpublished studies of the optical isomers of MDA and MDMA. It makes a fascinating story. The second question in this letter was also his second question.

This to Dr. Greer. (Excerpt)

"Your second question, the relationship between MDA and MDMA, is quite a bit more complex. In addressing this question I have spent some time rereading the pharmacological writings of both Nichols (at Purdue) and Glennon (at VCU at Richmond, VA), as well as reviewing my early clinical evaluations of both compounds. Just a couple of days ago I talked at length with Nichols on this very subject. Everything falls together into a consistent picture if one considers the following tenets:

(1) Almost all of the reported clinical and psychopharmacological properties reported for both MDA and MDMA have been on the so-called "racemic mixture" which is, by definition and in fact, a mixture in both cases of two different drugs which can be designated by the prefixes R- and S-, or levo- and dextro-. Thus in discussing the properties of racemic MDA and racemic MDMA, one must remember that one is discussing four drugs.

(2) In all psychedelic compounds that have been separated into these two components, the major active contributor to activity has been the R-form. (Let me use the uncomfortable term, "psychedelic" here for the MDA-type action, and the equally misleading term, "stimulant" for the MDMA-type action. This is unfairly simplistic, but will obviate the need of using quotation marks or giving explanations with every usage). This R-form-is-psychedelic is true not only for MDA, but for DOM, DOET, DOB and LSD as well (Anderson et al., 1978).

(3) In all stimulant compounds that have been separated into these two components, the major active contributor to activity has been the S-form. This S-form-is-stimulant is true for a wide range of compounds including amphetamine and methamphetamine.

(4) In those instances that a psychedelic drug has been N-methylated, the psychotropic activity is lost or greatly reduced

(Nichols and Glennon, 1984).

(5) In those instances where a stimulant drug has been N-methylated (such as with amphetamine or phentermine) the psychotropic activity has been maintained.

With that outline, let me try to give a picture of the four drugs under discussion. I have done some modest studies on the separated isomers of MDA which I have never published, but which are in general agreement with the findings (also in humans) of Marquandt (Syracuse). The R-isomer, in keeping with the other psychedelics studied, is the CNS-active one, showing the relatively long action of racemic MDA, and producing the sensory distortion and amplification associated with it. The S-isomer of MDA, even at dosages as high as 160 mg, produced a light CNS stimulation and excitement, but seemed devoid of the effects of the R-form. Reasonably, then, the racemate, being 50:50 R- and S-, gave a response largely dictated by the R-form. With MDMA, the study of the isomers gave quite a different picture (see Anderson et al., 1978). Here the S-MDMA was closely parallel to the racemate in both potency and quality, but R-MDMA was reduced in potency by a factor of at least three-fold. These relationships are summed up in this Table.

	Psychedelic action (the R-form)	Racemic mixture (50:50)	Stimulant action (the S-form)
MDA	R-MDA (120 mg), sensory harshness and long-lived.	RS-MDA (120 mg) 60 mg each form The R-form is predominant.	S-MDA (160 mg) more benign and peaceful.
MDMA	R-MDMA (200 mg), nearly inactive, 100 mg without any effects.	RS-MDMA (120 mg) 60 mg each form The S-form is predominant.	S-MDMA (120 mg) benign, with clear adrenergic effects.

I think that a careful reading of the several pharmacological studies that have been directed to these separate isomers will corroborate these conclusions, and that there can be little validity in an argument that the psychopharmacology of MDMA can be predicted from that of MDA. The facts as shown above simply don't support such an argument."

That is what I wrote him. I truly believe that MDMA must be considered upon its own merits, with a consideration of its risks and its rewards. Its chemical resemblance to MDA is an easy retreat for the busy administrator, but it is not valid clinically.

I hope that this information will be of some use to you. Please do not hesitate to write me, or call me by telephone (415) 934-4930 if I can provide you with any further factual information.

Sincerely yours,

Alexander T., Shulgin