UNITED STATES DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

In the Matter of	)	
	)	Docket No. 84-48
MDMA SCHEDULING	)	

Corrected Version

Response to Agency Exhibits B-21, B-22 and B-23 by Drs. Grinspoon et al.

The following represents a summary of observations by a number of scientists and researchers, and constitutes the comments submitted by Drs. Grinspoon, Greer et al. on Agency Exhibits B-21, B-22, and B-23.

Exhibit B-21A and B-21B -- Preliminary Report by Griffiths et al.

As a first general comment, we note that this study is based on work with three baboons. This low number of experimental subjects would generally not be satisfactory to draw significant conclusions, especially in view of the variability of the results that we discuss later. However, in spite of this problem, we will address our comments to the interpretation of results and methodology.

To the extent they show anything, the preliminary results of this study as now set out in Exhibit B-21B tend to show that MDMA does not have a high potential for abuse.

First, only two of the three baboons self-administered MDMA when the experiment was carried out according to its original protocol. In this connection, it should be noted that the study by Harris reported in Agency Exhibit B-23 produced a similar result -- only 2 of 3 rhesus monkeys in that study self-administered MDMA. Both of these studies, carried out in primates, indicate a high degree of variability and a lack of consistent self-administration. Note that, by contrast, in the present study (B-21) by Griffiths, all three baboons reliably self-administered cocaine. Thus, Griffiths study seems to indicate that while MDMA may have reinforcing properties, they are not as strong as those of cocaine and are variable, and are dependent on the dose and the individual animal tested.

Second, even when the baboons did self-administer, they did so at a lower level than for cocaine, amphetamines and phencyclidine. Indeed, the reinforcing properties of MDMA are less than those reported for diethylpropion, a Schedule IV substance. This comparison can be made using the data presented in the review article attached to Exhibit B-21 by Griffiths et al. entitled "Predicting the Abuse Liability of Drugs with Animal Drug Self-Administration Procedures: Psychomotor Stimulants and Hallucinogens," at p. 171 and the data in the present preliminary report.

Third, the data presented are not sufficient to determine whether the self-administration of MDMA by the baboons was statistically significant when compared to sa-

line. Previous studies of this nature reported in the article, entitled "Predicting the Abuse Liability of Drugs with Animal Drug Self-Administration Procedures: Psychomotor Stimulants and Hallucinogens," by Griffiths, Brady and Bradford (Advances in Behavioral Pharmacology, 1979) set out a range of saline self-administration values with which the mean value for the results of each dose of the tested compound are compared. On page 171 of that review article, the range of saline infusions per day for the 14 phenethylamines tested can be seen to consistently extend up to 4. The overlap of range values for saline and for the various doses of MDMA is an important consideration in the interpretation of results. In this preliminary report, there is no indication of this range of values. It is impossible to tell, therefore, whether self administration is in fact significantly elevated.

Fourth, the data in this preliminary study shows decreased self-administration for two baboons at higher doses. This data is consistent with the testimony that MDMA has built-in characteristics which make it unattractive to take higher doses or to take the drug repeatedly.

Fifth, when the authors of the study originally submitted their study (Exhibit B-21A), they themselves characterized MDMA's reinforcing efficacy as only "moderate." Mysteriously, and without explanation, when Exhibit B-21B was resubmitted to provide additional data points that had been omitted from the first paper, the authors revised their

characterization of MDMA's reinforcing efficacy to characterize it as "moderate to high." We submit the authors' original characterization is more credible as reflecting their view uninfluenced by the adversarial process, and more consistent with their data.*

The authors' final conclusion that "MDMA should be considered to be a compound having high abuse liability" is qualified in a critically important way. The authors justify that conclusion as being valid only if "MDMA does indeed have hallucinogenic activity." In fact, evidence presented in these hearings has shown that MDMA does not have

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* Without getting excessively technical, the scientific approach reflected in the changes made between Exhibit B-21A and Exhibit B-21B raise serious methodological questions. One new data point was added for baboon TA and one for baboon RA. Based on these new data points, the authors submit a revised interpretation that the results for the baboon labeled "TA" at doses 1.0 and 3.2 mg/kg/injection are now considered to be "artifacts" of the procedure. In the original report, these "artifacts" were interpreted as evidence that MDMA may have hallucinogenic activity.

If the order in which the doses were tested is responsible for this artifact, then was the experiment repeated using the correct order? If so, did the other points on the figure come out to be exactly the same as when the "artifacts" were observed? It is obvious that all the points on the two graphs are identical, with the exception of the one new test dose and the one retested dose. This means that the entire experiment was not repeated, but rather that one point was selected for retesting. What would the results have been if only the point that gave a high rate of self-administration was retested? Experiments simply cannot be carried out in this way. To retest only selected doses exposes a clear experimenter bias, in that some preconceived notion has been developed as to what that dose "should" have done. Thus, this retesting of a selected dose calls into question the validity of the whole experiment.

hallucinogenic activity. This is clear in both animal studies, using drug discrimination procedures with rats trained on known hallucinogens, and with reports from various psychiatrists who have supervised the human trials. These studies have all been offered as testimony during the course of these hearings. Griffiths et al. offer no references to support a claim that "MDMA does indeed have hallucinogenic activity as has been suggested in clinical trials." It is difficult to determine what they are referring to. However, we are unaware of any study that has established that MDMA is hallucinogenic, and the overwhelming evidence in this proceeding -- including statements directly from the FDA and the DEA -- is to the contrary. Therefore, if MDMA is not hallucinogenic, it appears that Griffiths would conclude that MDMA does not have a high abuse potential.

We have also emphasized, and this is also supported by testimony already presented during these hearings, that animal models cannot reliably predict whether a compound has hallucinogenic activity in humans. This is an assessment that can only be made by actual studies in humans.

Thus, while it is recognized that animal self-administration experiments represent a useful tool in studying the rewarding properties of drugs, interpretation of the results of these studies, especially with regard to the formulation of social policy, should proceed very carefully.

In Griffiths article, "Predicting the Abuse Liability of Drugs with Animal Drug Self-Administration Procedures: Psychomotor Stimulants and Hallucinogens," p. 174, which is attached to Exhibit B-21, he writes

> "Although these results would appear to suggest that drug self-administration procedures provide a valid estimate of abuse liability, it should be recognized that validation is greatly complicated by the fact that there are no generally accepted measures of drug abuse in the natural environment. Validation must necessarily involve assessment of results relative to the existing clinical literature available about the compounds."

Thus, Griffiths et al. themselves clearly note that animal studies must be validated by correlation with observed human and clinical use patterns.

Exhibit B-22 - Preliminary results from Dr. Seiden

It is exceedingly difficult to evaluate Seiden's work because so little data is provided. For example, while he notes that the "multiple injection experiments" involved doses at 10, 20 and 40 mg/kg, no information is provided on the dose levels of the single injection.

Nonetheless, even with the paucity of information, it is possible to point out the following.

First, MDMA in single doses was less toxic than MDA. That is very important since MDMA therapeutically is used only in single doses, and the evidence has indicated it is not used chronically even when taken recreationally.

Second, Dr. Seiden used only mega-doses of MDMA in order to obtain the effects in rat brains that he reports. Dr. Harris points out in Agency Exhibit B-23 that the LD-50 for injections in mice was about 20 mg/kg. Even assuming that the LD-50 is somewhat higher in rats, the doses that Seiden was using are enormous -- doses that are very significant percentages of the dose sufficient to kill the animals. Too much of anything can be harmful. Most toxicological effects have threshold effects and if one stays below the threshold, the adverse effect never appears. Human doses are 2 mg/kg taken orally. There can be no implication from Seiden's work that problems exist with the level of oral doses taken by humans.

Third, Dr. Seiden fails to compare his results with MDMA to other known drugs. What other drugs already on the market produce similar effects? What other drugs have been tested? With what results? What are the conclusions to be drawn? Without this information and analysis, Dr. Seiden's results really only suggest the need for further research.

In short, the significance of this study to humans is questionable. Several phenethylamines have similar neurotoxicity in rats. It has been documented in the literature, and in reports from the laboratory of Dr. Seiden, that the appetite suppressant agent fenfluramine, marketed under the trade name of Pondimin is very neurotoxic in rats, producing a pattern of serotonin depletion similar to that

observed for MDA or MDMA. The rat is an excellent model to observe this effect, but there is no current evidence that this has clinical relevance, or that fenfluramine has produced neurological deficits in man. The continued marketing of this compound, in spite of reports of neurotoxicity in the rat for at least seven years, attests to FDA's conclusion that this finding standing alone cannot be taken to have scientific significance.

Exhibit B-23 - Preliminary Report of Dr. Harris

This report is the most careful of the 3 studies in Exhibits B-21, B-22 and B-23.

Note that the study's conclusions are:

(1) MDMA is only one-third to one-fourth as potent as amphetamine;

(2) MDMA does not produce physical dependence;

(3) only 2 of 3 monkeys self-administered MDMA.

Dr. Harris himself notes that, while MDMA has "many" but not all the properties of sympathomimetic stimulants, it is less potent than amphetamines, does not appear to produce as intense an effect, and does not cause the loss of body weight that amphetamines does. Moreover, Dr. Harris notes only that MDMA "can" serve as a reinforcer, not that the evidence suggests it will do so. And he carefully concludes only that MDMA has a "significant" abuse potential -- not a high potential.

Dr. Harris notes that MDMA is more toxic than d-amphetamine. It should be emphasized that this applies to his studies in mice. A typical clinically effective dose of d-amphetamine in man would be 5-10 mg., as the sulfate salt. However, the typical dose of MDMA, as the hydrochloride, is in the range 75-150 mg., orally. If this dose of d-amphetamine sulfate were given to a drug-naive human subject, there would be considerable cardiovascular and behavioral toxicity. Thus, in humans, MDMA is both less potent than amphetamine as a stimulant, and is also less toxic.

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CERTIFICATE OF SERVICE

I certify that on November 4, 1985, a copy of the foregoing Response to Agency Exhibits B-21, B-22 and B-23 by Drs. Grinspoon et al. was delivered to the following:

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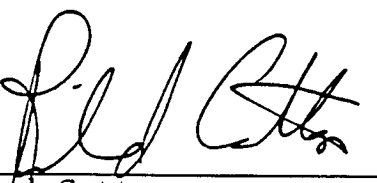

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