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Drug Enforcement Administration

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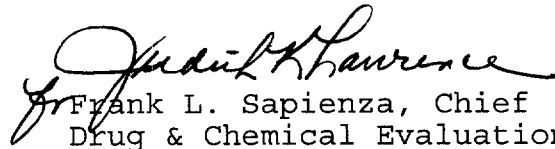
Docket Management Branch
(HFA-305)
Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, Maryland 20857

Dear Sir:

This is in reference to Docket No. 98N-0148 regarding the inclusion of isomers, esters, ethers and analogues of all substances in Schedules I and II of the 1971 Convention. The Drug Enforcement Administration (DEA) has reviewed the available data regarding the above substances. These data could be incorporated into the critical reviews to be used for the 31st World Health Organization (WHO) Expert Committee on Drug Dependence.

Enclosed is DEA's response to the questionnaire submitted to Member States by the Secretary-General of the United Nations pertaining to all substances in Schedules I and II of the 1971 Convention. The DEA is pleased to be providing such data to the Food and Drug Administration for inclusion in the U.S. submission to WHO for its critical review and prereview documents.

Sincerely,


Frank L. Sapienza, Chief
Drug & Chemical Evaluation Section

Enclosures

98N-0148

C6

Questionnaire for data collection for use by WHO & CND of the Economic and Social Council of the United Nations

1. Is there any licit manufacture of:

a) isomers, esters, ethers, and salts thereof of any of the substances in Schedules I and II of the 1971 Convention.

Isomers

For the purposes of this questionnaire that the term "isomers" will mean enantiomers and diastereomers of psychotropic substances which are not included in Schedules I and II of the 1971 Convention. There are six substances for which this holds true:

- (+)-cathinone
- (-)-lysergic acid diethylamide (LSD)
- (±)-isolysergic acid diethylamide (2 substances)
- (±)-*trans*-4-methylaminorex (2 substances)

For the purposes of this questionnaire, manufacture is defined according to the 1971 Convention as "all processes by which psychotropic substances may be obtained".

In the US, (+)-cathinone, (-)-lysergic acid diethylamide, (±)-isolysergic acid diethylamide (geometric isomer of LSD), and *cis*-4 methylaminorex are Schedule I controlled substances. *trans*-4-Methylaminorex is not controlled under the CSA.

In the United States, cathinone, LSD, and (±)-*trans*-4-methylaminorex are licitly manufactured for research and reference standards. The manufacturers do not stipulate whether or not specific isomers of the above substances are produced. Both isomers of cathinone are available in the US for use as analytical reference materials. Isolysergic acid is also available for the same purpose.

Esters and Ethers

For the purposes of this questionnaire, the licit manufacture of esters and ethers of the following substances was investigated: DMHP; parahexyl; THC; the six isomers of THC listed in Schedule I; psilocin; zipeprol.

The DEA has no information pertaining to the licit manufacture of esters of the above substances.

Small quantities of methyl ethers and related analogues of Δ 8-, Δ 9- and Δ 9,11-tetrahydrocannabinol were manufactured for pharmacological evaluation.. Ether analogues have

been manufactured for evaluation for their agonist and antagonist pharmacological properties in animal models.

b) a substance resulting from the modification of the chemical structure of substances already in Schedule I or II of the 1971 Convention?

For the purposes of this questionnaire, the term "analogues" will be utilized in place of the following phrase: "substances resulting from the modification of the chemical structure of substances already in Schedule I or II of the 1971 Convention". The definition of analogues will be similar to one utilized in the Controlled Substances Act (CSA) for the purposes of this questionnaire and will imply: a chemical structure similar to that of a controlled substance in Schedule I or II which produces a stimulant, depressant or hallucinogenic effect substantially similar to or greater than that produced by a Schedule I or II controlled substance.

The definition of amphetamine-like analogues would extend to substances such as ephedrine, pseudoephedrine, epinephrine, fenfluramine, dopamine...etc... that are utilized as licit pharmaceuticals, research substances and reference standards. These substances have an extensive legitimate market in the US. Using the above definitions, there would be hundreds of analogues of Schedule I and II psychotropic substances (See Shulgin, 1995). Many of these have been manufactured in small quantities in the United States for scientific and research activities. The following are some examples:

DEA has information pertaining to the licit manufacture of analogues and isomers of THC, from information submitted to DEA as part of research protocols and from information published in the scientific literature.

Six bromination products of the isomeric dimethoxyphenethylamines (hence, isomers of Nexus) were manufactured for analytical purposes in 1997.

For similar purposes, analogues of methoxy-MDA were synthesized from nutmeg oil and 3-methoxy-4,5-methylene-dioxybenzaldehyde (Clark et al, 1995).

A series of N-substituted 3,4-methylenedioxyphenyl-2-butanamines were synthesized for analytical and research purposes (Clark et al, 1995).

Metabolites and analogues of THC were prepared for research purposes (chemical synthesis, pharmacological evaluation) in the United States.

The methyl ether of bufotenine and hence a psilocin analogue was prepared for pharmacological evaluation and binding studies (Whitaker and Seeman, 1978).

p-Bromo and p-methoxy analogues of methylphenidate were manufactured (Thai et al, 1998) in the first reported asymmetric synthesis of methylphenidate and related substances.

Analogues of $\Delta 8$ -tetrahydrocannabinols with conformationally more-defined sidechains were manufactured (Papahatjis et al, 1998).

Benzofuran, indan and tetralin analogues of MDMA were synthesized and analyzed for pharmacological activity (Monte et al, 1993).

2. Has any abuse been reported of: a) such isomers, esters, ethers or salts?

Isomers

The DEA has not received any reports of abuse of (-)-lysergic acid diethylamide, (\pm)-isolysergic acid diethylamide, or (\pm)-*trans*-4-methylaminorex.

Esters or Ethers

DEA has had no reports of abuse of esters or ethers of psychotropic substances. None of the substances that are listed in the DEA System To Retrieve Information from Drug Evidence (STRIDE) database are esters or ethers of psychotropic substances.

It is unlikely that ethers of the tetrahydrocannabinol isomers will present a significant abuse problem. Research reports indicate that certain ether analogues of the cannabinoid drug class have minimal *in vivo* activity. The reports indicate that the phenolic hydroxyl is important for receptor recognition and *in vivo* potency (Compton *et al*, 1991). Another report indicates the molecular conformation of the methyl ether of $\Delta 9$ -THC is unlike that of $\Delta 9$ -THC and has great impact on its biological activity (Reggio, 1987).

b) a substance resulting from the modification of the chemical structure (analogues) of substances already in Schedule I or II of the 1971 Convention?

For reasons of abuse and trafficking, the United States has controlled the following substances which can be defined as analogues of psychotropic substances:

- MBDB, a positional isomer of N-Ethyl MDA. Additionally, all other positional isomers of hallucinogenic substances in Schedule I of the CSA
- 4-bromo-2,5-dimethoxyphenethylamine
- 5-methoxy-3,4-methylenedioxyamphetamine
- bufotenine
- 1-[(1-thienyl)cyclohexyl]pyrrolidine & other PCP analogues
- N,N-dimethylamphetamine

3. What is the degree of seriousness of the public health and social problems associated with such abuse? Examples of public health and social problems are acute intoxication, accidents, work absenteeism, mortality, behaviour problems, criminality, etc.

By virtue of the pharmacological similarity to parent compounds, abuse of many of the above substances can be expected to result in public health and social problems such as acute intoxication, accidents, work absenteeism, mortality, behaviour problems, and criminality. The risk to the public health has been evaluated for substances such as N,N-dimethylamphetamine, 2C-B, and PCP analogues and is contained in the control documents which are available from the Drug Enforcement Administration upon request.

4. Have there been seizures of any such substances in the illicit traffic during the previous three years? If so, what quantities were involved?

Isomers

- (+)-cathinone
- (-)-lysergic acid diethylamide (LSD)
- (±)-isolysergic acid diethylamide (2 substances)
- (±)-trans-4-methylaminorex (2 substances)

For the time period, 1/1/95 to 12/31/97 seizures for the following substances were reported in the DEA System To Retrieve Information from Drug Evidence.

Substance Name	Number of Seizures
cathinone ^a	9
l-lysergide	0
l-isolysergide	0
4-methylaminorex	0

^aisomers of cathinone not distinguished

Esters and Ethers

DEA does not have any information to demonstrate seizures of esters and ethers of psychotropic substances.

Analogues

The following information was reported in issues of Microgram, 1995-1997.

1. In 1997, An exhibit containing 0.1 g of white granular material was seized by the North Carolina Bureau of Investigation in Raleigh, North Carolina. The exhibit contained **5-methoxy-N,N-dimethyltryptamine** (an isomer of an ether of psilocin).
2. In 1997, the Forensic Science Service Metropolitan Laboratory in London, England reported the analysis of a number of tablets that contained **4-methylthioamphetamine** and caffeine. The tablets were mottled white, 14.0 mm in diameter, 4.7 mm thick and weighing 710 mg, single scored but with no other markings.
3. In 1995 and 1996, several seizures of tablets containing **MDEA (3,4-methylenedioxyethylamphetamine)**, **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** and **MDMMA (N,N-dimethyl-3,4-methylenedioxyamphetamine)** that originated from Holland were noted in Italy. The tablets had different markings: 1) pink tablets with a Fido-Dido" figure containing MDEA and MBDB; 2) white tablets with a "\$" figure containing MBDB; 3) beige tablets with a "bird" figure containing MDMMA.
4. In October 1996, the Florida Department of Law Enforcement, Orlando Regional Crime Laboratory seized two round white tablets with skull and crossbones on one side and "Killers" imprinted on the other side. The tablets contained round pink tablet with no markings that contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.
5. In July 1996, the New Jersey State Police, East Regional Laboratory, in Sea Girt reported receiving several white colored tablets bearing a "\$" logo. The tablets contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** on the basis of chemical analysis.
6. In June 1996, the Southwester Institute of Forensic Sciences in Dallas reported an exhibit of 19 white colored tablets bearing a "\$" imprint. Each tablet measured 10 mm in diameter and had an average weight of 300 mg. The tablets contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** on the basis of chemical analysis.
7. In June 1996, the Utah Department of Public Safety Criminalistics Laboratory, Salt Lake City, recently encountered an exhibit consisting of 180 mg of off-white solid. Chemical analysis revealed methamphetamine, amphetamine and N,N-dimethylamphetamine, possible **Ephedra-based methamphetamine**.
8. In April 1996, the New Mexico Department of Public Safety Southern Crime Laboratory, Mesilla Park reported an exhibit consisting of an 87 mg lump of white material. Chemical analysis revealed methamphetamine, amphetamine and N,N-dimethylamphetamine, an indication that the exhibit was synthesized from **Ephedra** rather than ephedrine or pseudoephedrine.
9. In February 1996, The Metropolitan Police Forensic Science Laboratory, London, U.K.

reported a 1.5 kg exhibit of inhomogeneous orange powder which was identified as **1-(4-methylphenyl)ethylamine** by chemical analysis.

10. In October 1996, the Iowa Division of Criminal Investigation Criminalistics laboratory, Des Moines identified **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** tablets (several). The tablets were round, white and bore a "\$" imprint.

11. In April 1996, the Israel National Police Division of Identification and Forensic Science in Jerusalem reported ten seizures totalling 150 tan, unscored tablets with "\$" imprint that contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** by laboratory analysis.

12. In January 1995, the North Carolina Bureau of Investigation in Raleigh reported the seizure of two exhibits of **bufotenine** (0.2g and 0.5g, respectively).

13. In April 1995, the Florida Department of Law Enforcement Regional Crime Laboratory in Ft. Meyers reported the seizure of 44 grayish-white single scored tablets bearing an image of the cartoon character "Fido-Dido". The tablets contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** by laboratory analysis.

14. In July 1995, the Ministerio De Sanidad Y Consumo Laboratory in Barcelona, Spain reported several submissions of white, single scored tablets bearing the "Fido-Dido" cartoon character imprint. The tablets contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**. In another submission the laboratory received white, single scored tablets without the cartoon character impression that also contained **MBDB**.

15. In September 1995, the Israel National Police Division of Identification and Forensic Science reported a seizure of 61 off-white "Fido Dido" tablets which contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

16. In September 1995, the Health Department of Spain, Laboratory of Drugs in the Balearic Islands reported an exhibit received in 1994 consisting of 10 grayish white tablets bearing the "Fido Dido" character and which contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

17. In November 1995, the Carabinieri Investigazioni Scientifiche Sottocentro laboratoria di Chimica in Parma, Italy reported several exhibits consisting of white single scored tablets with the "Fido Dido" cartoon character imprint and which contained **MBDB (N-methyl-1-(3,4-methylene-dioxyphenyl)-2-butanamine)**. Some of the tablets also contained caffeine.

18. In November 1995, the Florida Department of Law Enforcement's Regional Crime Laboratory in Tallahassee reported an encounter of 14 tan colored unscored tablets imprinted with "\$" and containing **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

19. In December 1995, the Ministerio de Sanidad Y Consumo, Laboratory de Drogas in Barcelona, Spain reported an exhibit of unscored tablets with "\$" imprinted on one side which contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

20. In March 1998, the Virginia Division of Forensic Science in Norfolk reported exhibits consisting of white tablets with "Scrooge McDuck" logo containing **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** and unmarked dark green tablets containing MDMA, MDEA and Nexus (**4-bromo-2,5-dimethoxyphenethylamine**). They also report three submissions of white tablets with a "Fido Dido" logo containing **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

21. In March 1998, the Virginia Division of Forensic Science in Roanoke reported two exhibits consisting of dark red tablets containing **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** and caffeine.

The following information was obtained from the DEA STRIDE database for the time period 01/01/95 to 12/31/97

Substance seized	Number of Seizures
Bufotenine	2
Chloroephedrine	2
d-Lysergic acid amylamide	0
d-Lysergic acid butylamide	0
d-Lysergic acid diisopropyl amide	0
d-2-Bromolysergide	0
Dimethamphetamine	1
Dipropyltryptamine	0
Fenfluramine	74
l-Methylpsilocybin	0
Mescaline	7
N-Butyl-1-phenylcyclohexylamine	0
N-isobutyl-1-phenylcyclohexylamine	0
1-Phenylcyclohexylmorpholine	0

3,4-Dimethoxyamphetamine	0
MBDB	0
2C-B	6
Tryptamine	0

5. Were such seized substances identified as being of local or foreign manufacture? Did they have any commercial markings?

See question #4, seizures reported in *Microgram*.

6. Was there any detection of clandestine laboratories manufacturing such substances?

In 1995-1996, most of the clandestine laboratories seized in the United States were producing methamphetamine. There were also a small number of methcathinone, amphetamine and phenyl-2-propanone laboratories seized. In past years, however, the Drug Enforcement Administration has identified the illicit manufacture of 2C-B, N,N-dimethylamphetamine and other amphetamine and tryptamine analogues.

Summary

The DEA has had relatively few encounters with isomers, esters, ethers and analogues of Psychotropic Substances. This is due, in part, to the passage of the Controlled Substances Analogue Enforcement Act of 1985 (see attached document). This act amended the Controlled Substances Act to allow for the criminal prosecution of those persons who intentionally marketed or distributed a controlled substances analogue for the purposes of avoiding controlled substances laws. This provided the U.S. Drug Enforcement officials with a proactive response to the problem of designer-drug trafficking. The analogue provision of the Controlled Substances Act has proven to be a successful instrument for attacking the problem of analogues and similar legislation that is in accord with individual legal systems could be considered by other countries.

References

- Compton, D.R.; Prescott, W.R., Jr.; Martin, B.R.; Siegel, C.; Gordon, P.M.; Razdan, R.K. "Synthesis and pharmacological evaluation of ether and related analogs of d8-, d9-, and d9,11-tetrahydrocannabinol." *J. Med. Chem.* 1991, 34, 3310-3316.
- Clark, R.C.; DeRuiter, J.; Noggle, F.T.; Valaer, A. "Identification of 1-(3,4-methylenedioxyphenyl)-2-butanamines related to MDMA." *Microgram*, 1995, 28, 154-168.
- Clark, C.R.; Noggle, F.T.; DeRuiter, J. "Analysis of methoxy MDA derivatives synthesized from nutmeg oil and 3-methoxy-4,5-methylenedioxybenzaldehyde." *Microgram* 1995, 28, 358-374.
- Davies, D.J.; Garratt, P.J.; Tocher, D.A.; Vonhoff, S. "Mapping the melatonin receptor. 5. Melatonin agonists and antagonists derived from tetrahydrocyclopent[b]indoles, tetrahydrocarbazoles and hexahydrocyclohept[b]indoles." *J. Med. Chem.* 1998, 41, 451-467.
- Monte, A.P.; Marona-Lewicka, D.; Cozzi, N.V.; Nichols, D.E. "Synthesis and pharmacological evaluation of benzofuran, indan, and tetralin analogues of 3,4-(methylenedioxy)amphetamine." *J. Med. Chem.* 1993, 36, 3700-3706.
- Papahatjis, D.P.; Kourouli, T.; Abadji, V.; Goutopoulos, A.; Makriyannis, A. "Pharmacophoreic requirements for Cannabinoid side chains: multiple bond and C1'-substituted Δ^8 -tetrahydrocannabinols." *J. Med. Chem.* 1998, 41, 1195-1200.
- Reggio, P.H.; "Molecular determinants for cannabinoid activity: refinement of a molecular reactivity template." *NIDA Res. Monogr.* 1987, 79, 82-95.
- Shulgin, A.; Shulgin, A; "PIHKAL A chemical love story" Transform Press, Berkeley, CA 1995, 978 pp.
- Thai, D.L.; Sapko, M.T.; Reiter, C.T.; Bierer, D.E.; Perel, J.M. "Asymmetric synthesis and pharmacology of methylphenidate and its para-substituted derivatives." *J. Med Chem.* 1998, 41, 591-601.
- Whitaker, P.M; Seeman, P. "High affinity 3H-serotonin binding to caudate: inhibition by hallucinogens and serotonergic drugs." *Psychopharmacology* 1978, 49, 1-5.