

PHENETHYLAMINES

Department of Health and Human Services

U. S. Government

5600 Fishers Lane

Rockville, Maryland, 20857

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PREFACE

This document is prepared in response to the WHO request for medical and scientific information on 30 phenethylamines.

Of the 30 phenethylamines requested, methoxyamphetamine and paramethoxyamphetamine are identical compounds; methoxymethylene-dioxyamphetamine and 5-methoxy-3,4-methylene-dioxyamphetamine are also identical compounds.

The table on page 0-3 is a summary of the available information on the phenethylamines. Information on diethylpropion (an analog of cathinone), phenmetrazine (an analog of fenbutrazate, and morazone), and mescaline (an analog of trimethoxyamphetamine and others) is provided for comparison purposes. All compounds are amphetamine-like CNS stimulants and/or LSD-like hallucinogens. The hallucinatory effects are associated with the serotonergic activation. The phenethylamines are arranged according to the chemical structures and the pharmacological profiles on page 0-4 through page 0-7, starting with CNS stimulants and ending with hallucinogens.

It is well established that no morphine-type physical dependence is associated with this class of compounds -- phenethylamines. It is also well-known that hallucinogenic substances, abused in man, are not self-administered in the experimental animals. Therefore, evaluation of abuse liabilities of these compounds should be based on the human data rather than on the animal data.

The following format is used throughout this document:

- I. Drug Name(s):
- II. Chemical Structure:
- III. Pharmacology and Abuse Profile:
 - A) Pharmacological Activities:
 - B) Scheduling:
 - C) Pre-clinical Abuse Liabilities:
 - D) Clinical Abuse Liabilities:
- IV. Journal Articles, Abstracts and Bibliography:

The information is based on a search of data banks on Medline, Toxline, and Excerpta Medicus from 1978 through 1983. Data on pre-clinical and clinical abuse liabilities are incomplete. It should not be interpreted that no abuse liabilities exist wherever the abuse data are not available.

Pagination starts with compounds numbered 1 through 30. These numbers are followed by a hyphen and a number started from 1. Under each compound, page 1 is a brief description of the compound. It is then followed by journal articles and bibliography.

Your comments on the usefulness of this document and your suggestions for improvement will be appreciated. Please mail your comments to Dr. Y. SHEU, NIDA, 5600 Fishers Lane, Rockville, Maryland 20857, USA.

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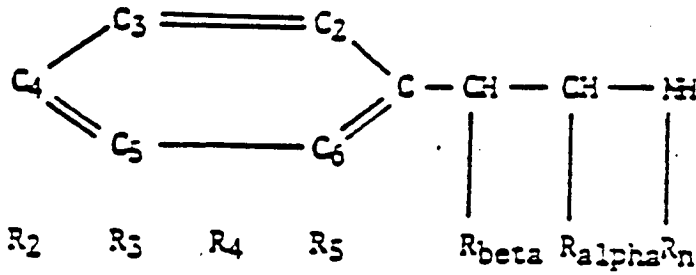
SUMMARY OF THE PHENETHYLAMINES

	Medical Use In USA	CSA Schedule	Year Enacted	Stimulant	Hallucinogen	Preclinical Abuse Liability	Clinical Abuse Liability
1. CATHINE	NO	NO		+			
2. CATHINONE	NO	NO		+			
3. CLOBENZorex	NO	NO		+		+	+
4. DIMETHOXYAMPHETAMINE	NO	NO		+			
5. DIMETHOXYBROMOAMPHETAMINE	NO	I	H 1973	+	+		
6. ETHYLAMPHETAMINE	NO	I	S 1982	+			
7. FENBUTRAZATE	NO	NO		+		+	
8. FENCAMFAMINE	NO	NO		+			
9. FENETHYLLINE	NO	I	S 1981	+		+	+
10. FENPROPorex	NO	NO		+			
11. FURFENorex	NO	NO		+			
12. LEVAMPHETAMINE	NO	NO		+			
13. LEVAMETHAMPHETAMINE	NO	II S	1970	+		+	
14. MEFENorex	YES	II S	1971	+		+	
15. METHOXYAMPHETAMINE* (See 19)	NO	NO		+			
16. METHOXYMETHYLENEDIOXYAMPHETAMINE† (See 29)	NO	I	H 1970		+	+	+
17. METHYLENEDIOXYAMPHETAMINE	NO	NO					
18. MCRAZONE	NO	I	H 1973	+	+		
19. PARA-METHOXYAMPHETAMINE*	NO	I	H 1973	+			
20. PARA-OXYAMPHETAMINE	YES	NO		+			
21. PEMOLINE	YES	IV S	1975	+			
22. PROPYLEXETERINE	YES	IV S	1975	+		-?	
23. PYROVALERONE	YES	NO		+			+
24. TRIMETHOXYAMPHETAMINE	NO	NO		+			
25. 4-BROMO-2,5-DIMETHOXYPHENETHYLAMINE	NO	I	H 1970		+		
26. 2,5-DIMETHOXY-4-ETHYLAMPHETAMINE	NO	NO			+		
27. N,N-DIMETHYLAMPHETAMINE	NO	NO		+			
28. N-ETHYL-3,4-METHYLENEDIOXYAMPHETAMINE	NO	NO		+			
29. 5-METHOXY-3,4-METHYLENEDIOXYAMPHETAMINE* NO	NO	I	H 1970		+		
30. 3,4-METHYLENEDIOXYMETHAMPHETAMINE	NO	NO			+		
DIETHYLPROPION	YES	IV S	1973	+		+	+
MESCALINE	NO	I	H 1970		+		
PHENMETRAZINE	YES	II S	1971	+		+	+

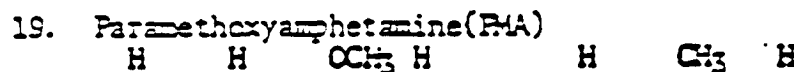
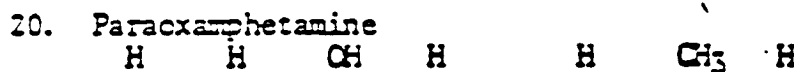
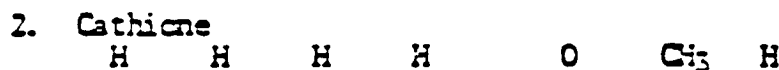
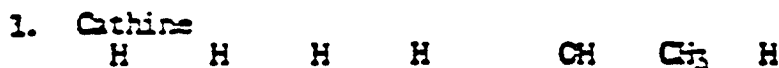
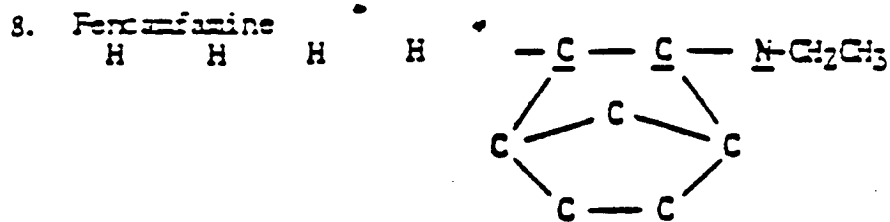
1: Over-the-counter preparations
 +: Positive report
 -: Negative report
 H: Hallucinogen
 *: 15 & 19 are identical compounds
 S: Stimulant
 CSA: The Controlled Substances Act (CSA) of the USA

I: Schedule I of CSA
 II: Schedule II of CSA
 IV: Schedule IV of CSA
 †: 16 & 29 are identical compounds
 1972: Year the law is enacted

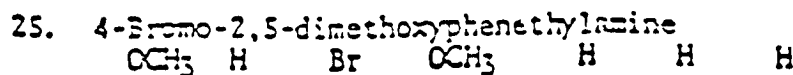
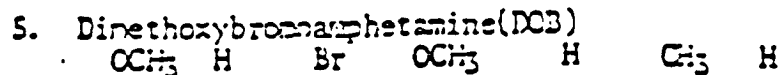
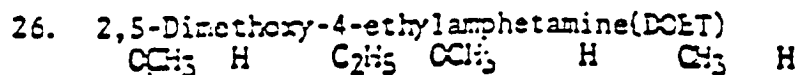
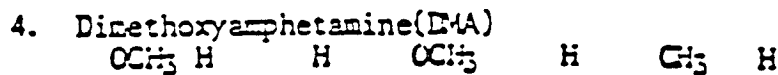
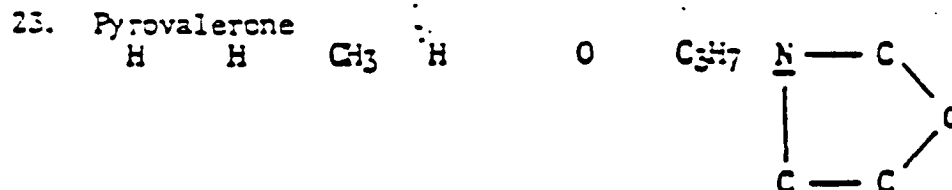
STRUCTURE AND PHARMACOLOGICAL PROFILE OF PHENETHYLAMINE



	R ₂	R ₃	R ₄	R ₅	R _{beta}	R _{alpha}	R _n
12. Levamfetamine	H	H	H	H	H	CH ₃	H
13. Levomethamphetamine	H	H	H	H	H	CH ₃	CH ₃
6. Ethylamphetamine	H	H	H	H	H	CH ₃	CH ₂ CH ₃
27. N,N-Dimethylamphetamine	H	H	H	H	H	CH ₃	(CH ₃) ₂
22. Propylhexedrine	H ₂	H ₂	H ₂	H ₂	H	CH ₃	CH ₃
10. Fenproporex	H	H	H	H	H	CH ₃	(CH ₂) ₂ CH
14. Mefenorex	H	H	H	H	H	CH ₃	(CH ₂) ₃ -Cl
3. Cloberzorex	H	H	H	H	H	CH ₃	$ \begin{array}{c} \text{CH}_2 - \text{C} - \text{C} = \text{C} \\ \parallel \quad \\ \text{C} - \text{C} = \text{C} \\ \\ \text{Cl} \end{array} $



15. Methoxyamphetamine (PMA)
See Paramethoxyamphetamine (PMA) (19)



Drug Abuse Warning Network

(DAWN)

Background

Project DAWN is a large-scale ongoing drug abuse data collection system sponsored by the National Institute on Drug Abuse (NIDA). The major objectives of this system are:

- to identify substances associated with drug abuse episodes that are reported by DAWN-affiliated facilities;
- to monitor drug abuse patterns and trends and to detect new abuse entities and new combinations;
- to assess health hazards associated with drug abuse; and
- to provide data for national, State and local drug abuse policy and program planning.

Methodology

A report is submitted for each drug abuse patient that visits a DAWN emergency room (ER) and each drug abuse death encountered by a DAWN medical examiner (ME). For the purpose of reporting to the DAWN system, drug abuse is defined as the non-medical use of a substance for psychic effect, dependence, or suicide attempt/gesture. Non-medical use includes:

- the use of prescription drugs in a manner inconsistent with accepted medical practice,
- the use of over-the-counter drugs contrary to approved labeling, or
- the use of any other substance (heroin, marijuana, peyote, glue, aerosols, etc.) for psychic effect, dependence, or suicide.

A drug abuse death usually involves a drug overdose, but the term may also be used to include deaths where drug usage was a contributory factor. In addition to drug overdose, a drug abuse emergency room episode may involve the chronic effects of habitual drug usage or unexpected reactions, i.e., the drug's effect was different than anticipated (e.g., causing hallucinations). Each report of a drug abuse episode includes demographic information about the patient or deceased, and information about the circumstances of the drug abuse episode. Up to six different substances can be specified for each episode.

Within each facility participating in the DAWN system, a designated DAWN reporter, usually a member of the emergency room or medical records staff, was responsible for identifying drug abuse episodes and recording and submitting data on each case. On a weekly basis, the total number of daily emergency room visits and deaths handled by medical examiners and the number of cases related to drug abuse were entered into a reporting log. From the official facility records, the relevant details of each drug abuse episode were transferred onto DAWN data forms.

In some instances, information on a drug abuse episode was reported some

time after the episode occurred. Reporting delays are common for medical examiners who may need to wait until the drug-relatedness of a death is ascertained and/or confirmed by complete lab tests or autopsy reports before filing their report. While ER data are virtually complete two months following the episode dates, ME data are approximately 80 percent complete after six months and fully complete after 12 months.

In 1982, DAWN data were collected from a non-random sample of emergency rooms and medical examiners in 26 metropolitan areas located throughout the continental United States. These metropolitan areas account for approximately one-third of the U.S. population. In addition, DAWN included a national panel of emergency rooms sampled from locations outside the 26 metropolitan areas. The metropolitan areas in the DAWN that were within the boundaries of the Standard Metropolitan Statistical Areas (SMSAs) as they were defined in 1972. In the San Francisco area, only hospitals in San Francisco County participate.

Data Limitations

There are several facets of DAWN data that need to be considered in order to avoid misinterpretation. First, DAWN collects information only about those drug abuse occurrences that have resulted in a medical crisis and have been subsequently identified as drug abuse episodes by a DAWN-affiliated facility. Further, while standard instruction manuals and training are provided to each DAWN reporter, the specific methods and procedures used to identify drug abuse episodes and substances may vary from facility to facility, particularly among the medical examiners. Some medical examiners may include cases involving circumstantial evidence. Other medical examiners may report only those drug abuse deaths confirmed through toxicologic analyses. Data from emergency rooms is based mostly on self reports, although some hospitals do obtain toxicological confirmation.

Since 1982 New York metropolitan area ME data are not included in this report, restrictions must be applied when observing patterns of medical examiner data at the total DAWN system level or comparing these data with data from previous years; in 1981, New York metropolitan area ME facilities accounted for 25 percent of the drug abuse deaths reported to DAWN. Also, it should be noted that medical examiner data for homicide-related drug abuse deaths are not included.

As mentioned earlier, since an episode may have up to six "drug mentions," not every reported substance is, by itself, necessarily a cause of the medical emergency, and should not be considered an abused drug. Alternately, the effects of some drugs may be of such a nature that non-medical use would not normally be expected to result in hospitalization. In addition, substances which contributed to a drug abuse episode may occasionally go unreported or undetected.

Multiple drug mentions per episode also have ramifications for coding drug-related variables. For example, since several drug use motives are sometimes associated with a multi-drug episode, and DAWN report forms do not provide for specific connections between motive and drug substance, some caution must be observed when relating drug mention patterns to specific motives.

Finally, since DAW facilities comprise a non-random sample, the data presented in this report reflect only those facilities which participated in DAW during all or part of 1962.

Attachment 5
MDMA DAWN DATA
Emergency Room Mentions

Total DAWN System (9-15-83)

<u>Date</u>	<u>Location</u>	<u>Alone/In Comb.</u>	<u>Motivation</u>	<u>Source</u>
2nd quarter, 1977	San Francisco, CA	In Comb.	Psych. eff./Dep.	Unk
4th quarter, 1977	"	" "	Unk	Unk
2nd quarter, 1978	Chicago, Ill.	" "	Suicide	Unk
"	San Francisco, CA	Alone	Psych. eff./Dep.	Street
"	"	"	" "	"
"	"	"	" "	Unk
4th quarter, 1979	"	"	Unk	Unk
1st quarter, 1981	Boston, Mass.	"	Suicide	Unk

Since the last DAWN mention in 1981, there has not been a single reported case of complications due to MDMA. This is remarkable in that an estimated 40,000 people per month are having MDMA experiences. In addition, during the 1979-1980 period several street samples of MDMA were analyzed by DEA laboratories and were found to be MDE. Since the DAWN reports are not based on chemical analysis of the reported material, it is possible that the MDMA mentions are not MDMA at all. They could perhaps be MDE, MDA or any number of other compounds.

It is also important to realize that in 1983, there were 1,915 DAWN reports involving over the counter sleeping aids, and 981 DAWN mentions of over the counter diet aids. Though these aids are much more widely used than MDMA, the intriguing question of relative abuse potential waits to be addressed.

Medical Examiner Mentions

<u>Date</u>	<u>Location</u>	<u>Alone/In Comb.</u>	<u>Motivation</u>	<u>Source</u>
3rd quarter, 1979	Seattle, Wash.	Alone	Psych. eff./Dep.	Unk

Age - 23

Race - White

Sex - Male

Manner of Death - Accidental/Unexpected

Cause of Death - Direct - single drug cause

Number of Drugs - 1

Support for cause of death - toxicology lab report, autopsy, physical sympt
statement by family or friend

Administration - oral

Means of ID - Blood, urine, other fluid/tissue

This case was investigated by Dr. Shulgin and his report follows. The cause of death is unknown, perhaps due to an epileptic seizure. Alcohol was also present, though omitted from the above medical examiners report. The presence of MDMA was not reliably established and therefore MDMA may not have been involved in this case at all.

There has been only one additional medical examiner report of a death linked to MDMA, the other one occurring April 14, 1985. Upon investigation by Dr. Shulgin it was determined that MDMA was not present at all in that case and that the report was an error in the DAWN system.