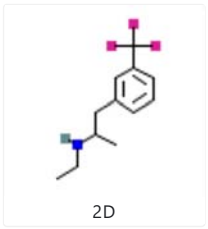
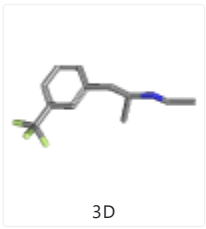
PubChem

REVIEWED
By Chris at 9:43 am, Mar 03, 2020

COMPOUND SUMMARY

Fenfluramine

PubChem CID:	3337
Structure:	 2D  3D Find Similar Structures
Chemical Safety:	 Acute Toxic  Irritant Laboratory Chemical Safety Summary (LCSS) Datasheet
Molecular Formula:	$C_{12}H_{16}F_3N$
Synonyms:	fenfluramine Fenfluraminum Obedrex Rotondin Pesos More...
Molecular Weight:	231.26 g/mol
Dates:	Modify: 2020-02-29 Create: 2005-03-25

Fenfluramine is an amphetamine derivative and a sympathomimetic stimulant with appetite-suppressant property. Fenfluramine, which was part of the Fen-Phen anti-obesity medication, stimulates the release of serotonin from vesicular storage, and modulates serotonin transporter function. Since serotonin regulates mood and appetite, among other functions, increased serotonin level results in a feeling of fullness and loss of appetite.

▶ NCI Thesaurus (NCIt)

Fenfluramine is a secondary amino compound that is 1-phenyl-propan-2-amine in which one of the meta-hydrogens is substituted by trifluoromethyl, and one of the hydrogens attached to the nitrogen is substituted by an ethyl group. It binds to the serotonin reuptake pump, causing inhbition of serotonin uptake and release of serotonin. The resulting increased levels of serotonin lead to greater serotonin receptor activation which in turn lead to enhancement of serotoninergic transmission in the centres of feeding behavior located in the hypothalamus. This suppresses the appetite for carbohydrates. Fenfluramine was used as the hydrochloride for treatment of diabetes and obesity. It was

withdrawn worldwide after reports of heart valve disease and pulmonary hypertension. It has a role as a serotonin uptake inhibitor, a serotonergic agonist and an appetite depressant. It is a secondary amino compound and a member of (trifluoromethyl)benzenes.

▸ ChEBI

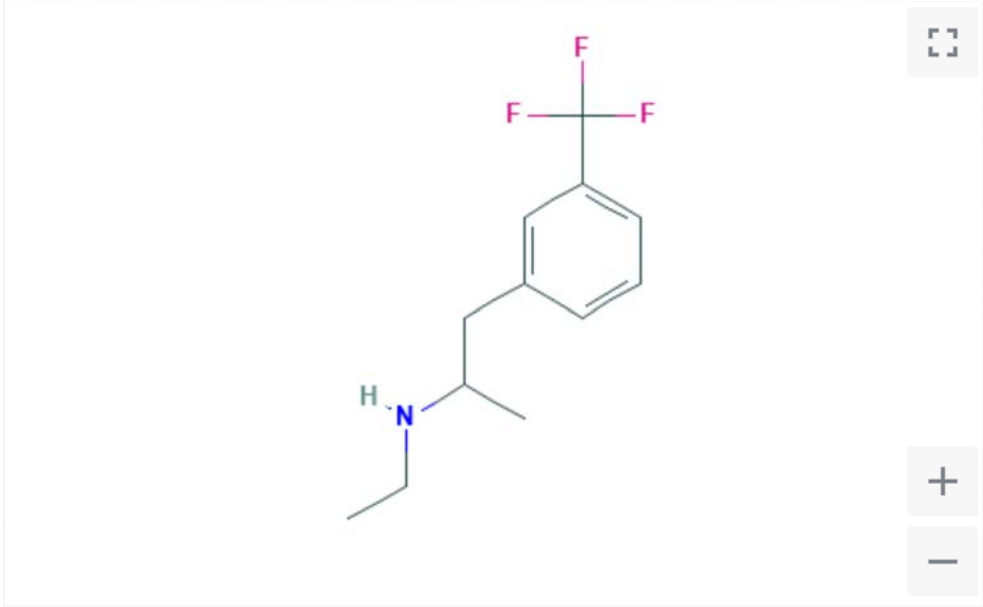
Fenfluramine is an appetite suppressant that was previously used in the treatment of obesity. After reports of heart valve disease and pulmonary hypertension, including a condition known as cardiac fibrosis, it was withdrawn from the U.S. market in 1997 due to safety reasons.

▸ DrugBank

1 Structures

1.1 2D Structure

Chemical Structure Depiction



PubChem

1.2 3D Conformer

PubChem

2 Names and Identifiers

2.1 Computed Descriptors

2.1.1 IUPAC Name

N-ethyl-1-[3-(trifluoromethyl)phenyl]propan-2-amine

Computed by LexiChem 2.6.6 (PubChem release 2019.06.18)

PubChem

2.1.2 InChI

InChI=1S/C12H16F3N/c1-3-16-9(2)7-10-5-4-6-11(8-10)12(13,14)15/h4-6,8-9,16H,3,7H2,1-2H3

Computed by InChI 1.0.5 (PubChem release 2019.06.18)

PubChem

2.1.3 InChI Key

DBGIVFWFUFKIQN-UHFFFAOYSA-N

Computed by InChI 1.0.5 (PubChem release 2019.06.18)

PubChem

2.1.4 Canonical SMILES

CCNC(C)CC1=CC(=CC=C1)C(F)(F)F

Computed by OEChem 2.1.5 (PubChem release 2019.06.18)

PubChem

2.2 Molecular Formula

$C_{12}H_{16}F_3N$

Computed by PubChem 2.1 (PubChem release 2019.06.18)

PubChem

2.3 Other Identifiers

2.3.1 CAS

458-24-2

ChemIDplus; DrugBank; EPA DSSTox; European Chemicals Agency (ECHA); HSDB

Related CAS

404-82-0 (hydrochloride)

- ChemIDplus

404-82-0

- European Chemicals Agency (ECHA)

2.3.1 Other CAS

5220-89-3, 25990-46-9

- ChemIDplus

2.3.2 European Community (EC) Number

206-968-2

- European Chemicals Agency (ECHA)

207-276-3

- European Chemicals Agency (ECHA)

2.3.3 DSSTox Substance ID

DTXSID4023044

- EPA DSSTox

2.3.4 Wikipedia

Fenfluramine

- Wikipedia

2.4 Synonyms

2.4.1 MeSH Entry Terms

Fenfluramine
Fenfluramine Hydrochloride
Fenfluramine Hydrochloride, (+-)-Isomer
Fenfluramine Hydrochloride, R Isomer
Fenfluramine Hydrochloride, R-Isomer
Fenfluramine, (+-)-Isomer
Fenfluramine, R Isomer
Fenfluramine, R-Isomer
Hydrochloride, Fenfluramine
Isomeride
Pondimin

MeSH

2.4.2 Depositor-Supplied Synonyms

fenfluramine	Fenfluramine [INN:BAN]	CHEBI:5000
Fenfluraminum	2-Ethylamino-1-(3-trifluoromethylphenyl)propane	N-Ethyl-alpha-methyl-3-(trifluoromethyl)benzenee
Obedrex	1-(meta-Trifluoromethyl-phenyl)-2 ethylaminopropane	Dexfenfluramina [Spanish]
Rotondin	N-Ethyl-alpha-methyl-3-trifluoromethylphenethylamine	Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifl
Pesos	HSDB 3080	C12H16F3N
Ponderax PA	N-ethyl-1-[3-(trifluoromethyl)phenyl]propan-2-amine	404-82-0
Fenfluramina	3-(Trifluoromethyl)-N-ethyl-alpha-methylphenethylamine	Fenfluramin
Adifax	S 768	Phenethylamine, N-ethyl-alpha-methyl-m-(trifluor
(+-)-Fenfluramine	EINECS 207-276-3	NCGC00159473-02
DL-Fenfluramine	DEA No. 1670	Acino
Fenfluramina [DCIT]	BRN 4783711	Benzeneethanamine, N-ethyl-.alpha.-methyl-3-(tri
458-24-2	N-Ethyl-alpha-methyl-m-(trifluoromethyl)phenethylamine	Dexfenfluramine [INN:BAN]
Fenfluraminum [INN-Latin]	Dexfenfluraminum [Latin]	Phenethylamine, N-ethyl-.alpha.-methyl-m-(trifluo

PubChem

3 Chemical and Physical Properties

3.1 Computed Properties

Property Name	Property Value	Reference
Molecular Weight	231.26 g/mol	Computed by PubChem 2.1 (PubChem release 2019.06.18)
XLogP3	3.4	Computed by XLogP3 3.0 (PubChem release 2019.06.18)
Hydrogen Bond Donor Count	1	Computed by Cactvs 3.4.6.11 (PubChem release 2019.06.18)
Hydrogen Bond Acceptor Count	4	Computed by Cactvs 3.4.6.11 (PubChem release 2019.06.18)
Rotatable Bond Count	4	Computed by Cactvs 3.4.6.11 (PubChem release 2019.06.18)
Exact Mass	231.123484 g/mol	Computed by PubChem 2.1 (PubChem release 2019.06.18)
Monoisotopic Mass	231.123484 g/mol	Computed by PubChem 2.1 (PubChem release 2019.06.18)
Topological Polar Surface Area	12 Å^2	Computed by Cactvs 3.4.6.11 (PubChem release 2019.06.18)
Heavy Atom Count	16	Computed by PubChem
Formal Charge	0	Computed by PubChem
Complexity	203	Computed by Cactvs 3.4.6.11 (PubChem release 2019.06.18)
Isotope Atom Count	0	Computed by PubChem
Defined Atom Stereocenter Count	0	Computed by PubChem
Undefined Atom Stereocenter Count	1	Computed by PubChem
Defined Bond Stereocenter Count	0	Computed by PubChem
Undefined Bond Stereocenter Count	0	Computed by PubChem
Covalently-Bonded Unit Count	1	Computed by PubChem
Compound Is Canonicalized	Yes	Computed by PubChem (release 2019.01.04)

PubChem

3.2 Experimental Properties

3.2.1 Boiling Point

108-112 °C at 12 mm Hg

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 703

HSDB

3.2.2 Melting Point

108-112 °C at 1.20E+01 mm Hg

DrugBank

3.2.3 Solubility

412 mg/L

- DrugBank

In water, 412 mg/L at 25 °C (est)

US EPA; Estimation Program Interface (EPI) Suite. Ver.3.12. November 30, 2004. Available from, as of Oct 4, 2005: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

- HSDB

3.2.4 Vapor Pressure

4.1X10-2 mm Hg at 25 °C (est)

US EPA; Estimation Program Interface (EPI) Suite. Ver.3.12. November 30, 2004. Available from, as of Oct 4, 2005: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

- HSDB

3.2.5 Octanol/Water Partition Coefficient

3.36

SANGSTER (1993)

- DrugBank

3.36 (LogP)

SANGSTER (1993)

- EPA DSSTox

log Kow = 3.36

Sangster J; LOGKOW Databank. Sangster Res. Lab., Montreal Quebec, Canada (1993)

- HSDB

3.2.6 Stability/Shelf Life

Generally stable under ordinary conditions in light, air, & heat /Hydrochloride/

Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 823

- HSDB

3.2.7 Decomposition

When heated to decomp it emits very toxic fumes of fluoride ion and oxides of nitrogen.

Sax, N.I. Dangerous Properties of Industrial Materials. 6th ed. New York, NY: Van Nostrand Reinhold, 1984., p. 1376

- HSDB

3.2.8 Dissociation Constants

pKa = 9.6 at 25 °C (est)

Hilal SH et al; pp. 291-353 in Quantitative Treatments of Solute/Solvent Interactions: Theoretical and Computational Chemistry Vol. 1 NY, NY: Elsevier (1994). SPARC pKa/property server Available from, as of Oct 14, 2005: http://ibmlc2.chem.uga.edu/sparc/

▶ HSDB

3.2.9 Kovats Retention Index

Standard non-polar	1220, 1220, 1220, 1240, 1226, 1220, 1240.8, 1218.2, 1222, 1220, 1220
Semi-standard non-polar	1240.6, 1183, 1183, 1228.4, 1227, 1232.2, 1233.8, 1224, 1239.7, 1173, 1177, 1185
Standard polar	1531, 1532, 1555, 1562, 1569

▶ NIST Mass Spectrometry Data Center

3.2.10 Other Experimental Properties

White to off-white amorphous powder; does not exhibit polymorphism; melts with 2 degree range between 165-170 °C; pKa 9.92; characteristic odor; sparingly soluble in water & ethanol /Fenfluramine hydrochloride/

Osol, A. and J.E. Hoover, et al. (eds.). Remington's Pharmaceutical Sciences. 15th ed. Easton, Pennsylvania: Mack Publishing Co., 1975., p. 823

▶ HSDB

Crystals from ethanol and ether; mp: 166 °C /Hydrochloride/

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 703

▶ HSDB

Specific optical rotation: 9.5 deg at 25 °C/D (concentration by volume= 8 g in 100 ml ethanol) /dextro-Fenfluramine/

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 703

▶ HSDB

Crystals from ethyl acetate; mp: 160-161 °C /dextro-Fenfluramine hydrochloride/

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 703

▶ HSDB

Specific optical rotation: -9.6 deg at 25 °C/D (concentration by volume= 8 g in 100 ml ethanol) /levo-Fenfluramine/

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 703

▶ HSDB

Crystals from ethyl acetate; mp: 160-161 °C /levo-Fenfluramine hydrochloride/

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 703

▶ HSDB

Henry's Law constant = 2.7X10-5 atm-cu m/ mol at 25 °C (est)

US EPA; Estimation Program Interface (EPI) Suite. Ver.3.12. November 30, 2004. Available from, as of Oct 4, 2005: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

▶ HSDB

Hydroxyl radical reaction rate constant = 3.3X10-11 cu cm/molec-sec at 25 °C (est)

US EPA; Estimation Program Interface (EPI) Suite. Ver.3.12. November 30, 2004. Available from, as of Oct 4, 2005: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

▶ HSDB

4 Spectral Information

4.1 Mass Spectrometry

Showing 2 of 8 View More

MoNA ID	FiehnHILIC000350
MS Category	Experimental
MS Type	Chromatography identified as LC-MS
MS Level	MS2
Precursor Type	[M+H]+
precursor m/z	232.1304
Instrument	Thermo Q Exactive HF
Instrument Type	LC-ESI-QFT
Ionization Mode	positive
Collision Energy	HCD (NCE 20-30-40%)
Splash	splash10-0a59-0960000000-89cd96ada4fa63c405a7
Thumbnail	
Submitter	Megan Showalter, University of California, Davis

MassBank of North America (MoNA)

MoNA ID	FiehnHILIC000351
MS Category	Experimental
MS Type	Chromatography identified as LC-MS
MS Level	MS2
Precursor Type	[M+H]+
precursor m/z	232.1306
Instrument	Thermo Q Exactive HF

Instrument Type	LC-ESI-QFT
Ionization Mode	positive
Collision Energy	HCD (NCE 20-30-40%)
Splash	splash10-0a59-0960000000-664edaae5fd4931ad0b4
Thumbnail	
Submitter	Megan Showalter, University of California, Davis

MassBank of North America (MoNA)

4.1.1 GC-MS

Showing 2 of 7 View More

NIST Number	250583
Library	Main library
Total Peaks	169
m/z Top Peak	72
m/z 2nd Highest	44
m/z 3rd Highest	159
Thumbnail	

NIST Mass Spectrometry Data Center

NIST Number	125735
Library	Replicate library
Total Peaks	73
m/z Top Peak	72
m/z 2nd Highest	44
m/z 3rd Highest	159
Thumbnail	

NIST Mass Spectrometry Data Center

4.1.2 MS-MS

Showing 2 of 5 View More

NIST Number	1004441
Instrument Type	IT/ion trap
Collision Energy	0
Spectrum Type	MS2
Precursor Type	[M+H]+
Precursor m/z	232.1308
Total Peaks	7
m/z Top Peak	232
m/z 2nd Highest	233

m/z 3rd Highest	187
Thumbnail	

NIST Mass Spectrometry Data Center

NIST Number	1004446
Instrument Type	IT/ion trap
Collision Energy	0
Spectrum Type	MS2
Precursor Type	[M+H]+
Precursor m/z	232.1308
Total Peaks	9
m/z Top Peak	159
m/z 2nd Highest	232
m/z 3rd Highest	233
Thumbnail	

NIST Mass Spectrometry Data Center

4.1.3 Other MS

Other MS	Intense mass spectral peaks: 72 m/z, 159 m/z, 216 m/z, 230 m/z

HSDB

4.2 IR Spectra

4.2.1 ATR-IR Spectra

Instrument Name	Bio-Rad FTS
Technique	ATR-Film (MeCl2) (DuraSamplIR II)
Source of Spectrum	Forensic Spectral Research
Source of Sample	Alltech Associates, Inc., Grace Davison Discovery Sciences
Catalog Number	1798
Lot Number	27082
Copyright	Copyright © 2012-2018 Bio-Rad Laboratories, Inc. All Rights Reserved.
Thumbnail	

SpectraBase

5 Related Records

5.1 Related Compounds with Annotation

PubChem

5.2 Related Compounds

Same Connectivity	6 Records
Same Stereo	4 Records
Same Isotope	3 Records
Same Parent, Connectivity	62 Records
Same Parent, Stereo	49 Records
Same Parent, Isotope	58 Records
Same Parent, Exact	45 Records
Mixtures, Components, and Neutralized Forms	93 Records
Similar Compounds	818 Records
Similar Conformers	2,385 Records

PubChem

5.3 Substances

5.3.1 Related Substances

All	237 Records
Same	72 Records

Mixture	165 Records

PubChem

5.3.2 Substances by Category

PubChem

5.4 Entrez Crosslinks

PubMed	814 Records
Taxonomy	3 Records
OMIM	52 Records
Gene	9 Records

PubChem

5.5 Associated Chemicals

Fenfluramine hydrochloride;404-82-0

HSDB

5.6 NCBI LinkOut

NCBI

6 Chemical Vendors

- PubChem

7 Drug and Medication Information

7.1 Drug Indication

For the management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction.

- DrugBank

Adjunctive therapy to diet, in patients with obesity and a body mass index (BMI) of 30 kg/m2 or higher who have not responded to an appropriate weight-reducing regimen alone

- EU Community Register of Medicinal Products

7.2 Clinical Trials

7.2.1 ClinicalTrials.gov

- ClinicalTrials.gov

7.2.2 EU Clinical Trials Register

EU Clinical Trials Register

7.3 Therapeutic Uses

The Food and Drug Administration, acting on ... evidence about significant side-effects associated with fenfluramine and dexfenfluramine, has asked the manufacturers to voluntarily withdraw both treatments for obesity from the market. ... Both companies have agreed to voluntarily withdraw their drugs. The FDA is not requesting the withdrawal of phentermine, the third widely used medication for obesity. The action is based on ... findings from doctors who have evaluated patients taking these two drugs with echocardiograms, a special procedure that can test the functioning of heart valves. These findings indicate that approximately 30 percent of patients who were evaluated had abnormal echocardiograms, even though they had no symptoms. This is a much higher than expected percentage of abnormal test results.

US FDA; Center for Drug Evaluation and Research; FDA Announces Withdrawal Fenfluramine and Dexfenfluramine. For Immediate Release - September 15, 1997. Washington, DC: Food Drug Admin. Available from, as of October 12, 2005: http://www.fda.gov/cder/news/phen/fenphenpr81597.htm

HSDB

Appetite Depressants; Serotonin Agents; Serotonin Uptake Inhibitors

National Library of Medicine's Medical Subject Headings online file (MeSH, 1999)

HSDB

Adjunct to caloric restriction in the short term treatment (a few weeks) of exogenous obesity. /Use is included in the labeling approved by the US Food and Drug Administration. /Fenfluramine hydrochloride/

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

HSDB

7.4 Drug Warnings

Temporal association between use of fenfluramine (Pondimin) or dexfenfluramine (Redux) and the development of unusual mitral, aortic, tricuspid, and/or pulmonary valvular (usually multivalvular) and echocardiographic abnormalities (that sometimes occurred concomitantly with pulmonary hypertension, occasionally required open heart surgery, and rarely were fatal) resulted in the withdrawal of /this/ anorexigenic agents from the US market in 1997.

McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2005. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2005 (Plus Supplements)., p. 2357

HSDB

Fenfluramine is contraindicated in patients with severe hypertension, glaucoma, or symptomatic cardiovascular disease including arrhythmias, and in those with known hypersensitivity to fenfluramine or other sympathomimetic amines. Fenfluramine is contraindicated during or within 14 days of administration of monoamine oxidase inhibitors. The drug is also contraindicated in patients with a history of drug abuse. Fenfluramine should not be administered to patients with alcoholism, since adverse psychiatric effects (e.g., psychosis) may occur.

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

HSDB

Although some clinical studies have reported the use of fenfluramine in obese children, its safety and efficacy in pediatric patients have not been established and fenfluramine is not recommended for use in children younger than 12 years of age.

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

HSDB

General anesthetics should be administered with caution to patients receiving fenfluramine prior to surgery, since the drug may have catecholamine depleting effects following prolonged administration. If general anesthesia cannot be avoided, cardiac monitoring and facilities for cardiac resuscitation are essential during surgery in these patients.

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1771

HSDB

For more Drug Warnings (Complete) data for FENFLURAMINE (14 total), please visit the HSDB record page.

HSDB

7.5 Reported Fatal Dose

The lowest reported fatal dose of fenfluramine hydrochloride was 400 mg in a small child and the highest reported nonfatal dose was 1.8 g in an adult.

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1771

HSDB

8 Pharmacology and Biochemistry

8.1 Pharmacology

Used to treat obesity, Fenfluramine decreases caloric intake by increasing serotonin levels in the brain's synapses. Fenfluramine acts as a serotonin reuptake inhibitor. It also causes release of serotonin from the synaptosomes. This in turn increases serotonin transmission in the feeding centre of the brain which suppresses appetite.

▶ DrugBank

Fenfluramine is an amphetamine derivative and a sympathomimetic stimulant with appetite-suppressant property. Fenfluramine, which was part of the Fen-Phen anti-obesity medication, stimulates the release of serotonin from vesicular storage, and modulates serotonin transporter function. Since serotonin regulates mood and appetite, among other functions, increased serotonin level results in a feeling of fullness and loss of appetite.

▶ NCI Thesaurus (NCIt)

8.2 MeSH Pharmacological Classification

Serotonin Uptake Inhibitors

Compounds that specifically inhibit the reuptake of serotonin in the brain. (See all compounds classified as Serotonin Uptake Inhibitors.)

▶ MeSH

Serotonin Agents

Drugs used for their effects on serotonergic systems. Among these are drugs that affect serotonin receptors, the life cycle of serotonin, and the survival of serotonergic neurons. (See all compounds classified as Serotonin Agents.)

▶ MeSH

8.3 ATC Code

A - Alimentary tract and metabolism

A08 - Antiobesity preparations, excl. diet products

A08A - Antiobesity preparations, excl. diet products

A08AA - Centrally acting antiobesity products

A08AA02 - Fenfluramine

▶ WHO ATC

8.4 Absorption, Distribution and Excretion

Absorption

Fenfluramine is well-absorbed from the gastrointestinal tract, and a maximal anorectic effect is generally seen after 2 to 4 hours.

DrugBank

Postmortem blood concentrations in one adult and three children ranged from 6.5 to 16 mg/L. A fenfluramine hair level of 14.1 ng/mg was demonstrated in an overdose fatality.

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 875

HSDB

Fenfluramine is widely distributed into tissues with a Vd of 12 to 16 L/kg. ... Excretion of the parent compound is enhanced in acidic urine.

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 874

HSDB

Fenfluramine is widely distributed in almost all body tissues. Autoradiographic studies in rats showed highest concentrations of the drug in stomach and intestine; lower concentrations were found in lungs, liver, brain and spinal cord, and bone marrow. In monkeys, fenfluramine and its de-ethylated metabolite cross the placental barrier. It is not known whether fenfluramine is distributed into milk.

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

HSDB

Following oral administration, fenfluramine hydrochloride is readily absorbed from the GI tract. Correlation of blood concentrations with clinical effects has not been established. ... The rate of urinary excretion depends on urinary flow rate and pH ... Fenfluramine is also excreted in saliva and sweat to a small extent. /Fenfluramine hydrochloride/

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

HSDB

8.5 Metabolism/Metabolites

Hepatic.

DrugBank

Fenfluramine hydrochloride is metabolized to norfenfluramine by de-ethylation; this metabolite is further deaminated and oxidized to m-trifluoromethylbenzoic acid. The drug is excreted principally in the urine as m-trifluoromethylhippuric acid, a glycine conjugate of m-trifluoromethylbenzoic acid, and smaller quantities of norfenfluramine and unchanged drug. There are wide interindividual variations in rates of biotransformation and elimination of fenfluramine and its metabolites... /Fenfluramine hydrochloride/

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

HSDB

/Fenfluramine/ is metabolized in the liver by N-dealkylation to the active metabolite norfenfluramine. Less than 15% of a therapeutic dose is excreted as parent compound or active metabolite; the remainder is nonactive benzoic acid and alcohol derivatives. ...

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 874

HSDB

99% of cerebral fenfluramine was dealkylated to norfenfluramine. N-acetylnorfenfluramine & m-trifluoromethyl hippuric acid were identified as cerebral metabolites.

Sherman AD, Gal EM; Cerebral Metabolism of Intraventricular (3)H-Fenfluramine; Neuropharmacology 16 (5): 309-15 (1977)

▶ HSDB

8.6 Biological Half-Life

20 hours

▶ DrugBank

In one study, the mean elimination half-life of fenfluramine in patient with uncontrolled pH was about 20 hr while elimination half-life was about 11 hr when an acidic urinary pH was maintained. /Fenfluramine hydrochloride/

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

▶ HSDB

Considerable first-pass effect due to rapid n-dealkylation of fenfluramine is apparent after per os doses. Rapid metabolism of derivative n-(2-benzoyloxyethyl)norfenfluramine has also been reported in man with apparent biological t/2 for total drug material of about 2 hr.

The Chemical Society. Foreign Compound Metabolism in Mammals Volume 3. London: The Chemical Society, 1975., p. 158

▶ HSDB

The half life of fenfluramine is 13 to 30 hours and is urine pH dependent. ...

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 875

▶ HSDB

8.7 Mechanism of Action

Fenfluramine binds to the serotonin reuptake pump. This causes inhbition of serotonin uptake and release of serotonin. The increased levels of serotonin lead to greater serotonin receptor activation which in turn lead to enhancement of serotoninergic transmission in the centres of feeding behavior located in the hypothalamus. This suppresses the appetite for carbohydrates.

▶ DrugBank

The exact mechanism of action of fenfluramine has not been clearly defined. Results of animal studies indicate that its appetite-inhibiting may result from stimulation of the ventromedial nucleus of the hypothalamus. The mechanism by which this stimulation is mediated has not yet been determined. Although fenfluramine is used in the treatment of obesity as an anorexigenic, it has not been firmly established that the pharmacologic action is principally one of appetite suppression; other CNS actions and/or metabolic effects may be involved. ... Cardiovascular and autonomic effects produced by fenfluramine in animals appear to be qualitatively similar to those of amphetamine, but as a pressor agent it is 10-20 times less potent than dextroamphetamine. Some clinical studies have shown fenfluramine to have hypotensive effects in obese hypertensive patients. EEG studies, both awake and during sleep, show fenfluramine to be qualitatively different from amphetamine and other amphetamine congeners and suggest that fenfluramine may be more similar to sedative psychotherapeutic drugs rather than CNS or cerebral stimulants. There is some evidence that fenfluramine interferes with CNS pathway which regulate the release of human growth hormone.

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

▶ HSDB

The neurochemical mechanisms by which drugs acting on central serotoninergic system modify feeding were reviewed. Fenfluramine, a clinically effective appetite suppressant, releases serotonin from nerve terminals and inhibits its reuptake, and considerable evidence suggests that these effects mediate its anorectic activity. The D isomer of fenfluramine is particularly specific in affecting serotonin mechanisms and causing anorexia. Transmitters other than serotonin such as acetylcholine, catecholamines and GABA are also affected by systemic administration of fenfluramine, but some of these effects are secondary to fenfluramine's action on serotoninergic mechanisms. Moreover, there is no evidence that these brain substances are involved in fenfluramine's ability to cause anorexia. Several studies with drugs affecting different serotonin mechanisms such as release and uptake or mimicking the action of serotonin at post-synaptic receptors suggest that increase serotonin release and direct stimulation of postsynaptic receptors are the most effective mechanisms for causing depression of food intake, although inhibition of serotonin uptake may also contribute in appropriate conditions. Development of serotonin receptor hyposensitivity and, in some instances, decreased serotonin levels may lead to tolerance to the anorectic activity of drugs enhancing serotonin transmission, the degree of this depending critically on the type of effect on serotonin mechanisms and intensity and duration of serotonin receptor activation. Recent evidence suggests that a decrease in serotonin function causes stimulation of feeding. This may lead to development of new strategies for the treatment of clinical anorexias.

PMID:2427023
Garattini S et al; Appetite 7 Suppl: 15-38 (1986)

▶ HSDB

9 Use and Manufacturing

9.1 Use Classification

EU Pharmaceutical Product Classes	Human drug

▶ EU Community Register of Medicinal Products

9.2 Uses

EPA CPDat Chemical and Product Categories

▶ EPA Chemical and Products Database (CPDat)

MEDICATION

▶ HSDB

Appetite suppressant for the short-term (a few weeks) management of obesity. /Former use/

FDA: Center for Drug Evaluation and Research; Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux). Available from, as of March 30, 2006: http://www.fda.gov/cder/news/phen/fenphenqa2.htm

▶ HSDB

9.3 Methods of Manufacturing

Preperation of optical isomers: US 3198834 (1965 to Sci. Union et Cie Soc. Franc. Recherche Med.)

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 703

▶ HSDB

Preperation: L.G Beregi et al., FR M1658; eidem US 3198833 (1965 to Sci. Union et Cie Soc. Franc. Recherche Med.)

O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 703

HSDB

Fenfluramine is prepared by reductive alkylation of norfenfluramine with acetaldehyde [18]. The nor compound is obtained by catalytic hydrogenation of the oxime made from 3-trifluoromethylphenyl acetone.

Ullmann's Encyclopedia of Industrial Chemistry. 6th ed.Vol 1: Federal Republic of Germany: Wiley-VCH Verlag GmbH & Co. 2003 to Present, p. V3 624 (2003)

HSDB

9.4 Formulations/Preparations

Fenfluramine hydrochloride (Pondimin), 20 mg tablets ... /Fenfluramine hydrochloride; Former formulation/

Goodman, L.S., and A. Gilman. (eds.) The Pharmacological Basis of Therapeutics. 5th ed. New York: Macmillan Publishing Co., Inc., 1975., p. 510

HSDB

10 Identification

10.1 Clinical Laboratory Methods

Gas liquid chromatographic determination of fenfluramine in plasma.

Lindley TN, Sharman JR; Nzj Med Lab Technol 31 (3): 69-71 (1977)

HSDB

Gas chromatographic/mass spectrometric identification of metabolites of amphetamines & analogs.

Coutts RT; Can Res 10 (3): 23, 25, 27-8 (1977)

HSDB

Fenfluramine recovered from urine & identified by gas chromatography.

Campbell DB; Methodol Dev Biochem 5: 105-6 (1976)

HSDB

Simultaneous determination of fenfluramine & norfenfluramine in human plasma & urine by a gas-liquid chromatographic-electron capture detector assay.

Midha KK et al; Can J Pharm Sci 14 (1): 18-21 (1979)

HSDB

Reagents, methods, and kits for an amphetamine class fluorescence polarization immunoassay.

Brynes PJ et al; Eur Pa Appl Patent No. 399184 (11/28/90) (Abbott Labs)

HSDB

A capillary column gas chromatographic method for the identification of drugs of abuse in urine samples. /Fenfluramine is one of the substances identified/.

Caldwell R, Challenger H; 26 (5): 430-43 (1989)

HSDB

11 Safety and Hazards

11.1 Hazards Identification

11.1.1 GHS Classification

Showing 1 of 2 View More

Pictogram(s)	 Acute Toxic Irritant
Signal	Danger
GHS Hazard Statements	Aggregated GHS information provided by 2 companies from 2 notifications to the ECHA C&L Inventory. Each notification may be associated with multiple companies. H300 (50%): Fatal if swallowed [Danger Acute toxicity, oral] H302 (50%): Harmful if swallowed [Warning Acute toxicity, oral] Information may vary between notifications depending on impurities, additives, and other factors. The percentage value in parenthesis indicates the notified classification ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown.
Precautionary Statement Codes	P264, P270, P301+P310, P301+P312, P321, P330, P405, and P501 (The corresponding statement to each P-code can be found at the GHS Classification page.)

European Chemicals Agency (ECHA)

11.2 Handling and Storage

11.2.1 Storage Conditions

Tablets should be stored in well-closed containers between 15 to 30 °C. /Fenfluramine hydrochloride/

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1769

HSDB

11.3 Regulatory Information

11.3.1 FDA Requirements

Fenfluramine used as a anorectic was marketed in the United States in 1973.

U.S. Department of Health and Human Services. Public Health Service. FDA. Drug Utilization in the United States: 1989. Eleventh Annual Review. p.17 (April, 1991)

HSDB

Drug products withdrawn or removed from the market for reasons of safety or effectiveness. The following drug products were withdrawn or removed from the market because such drug products or components of such drug products were found

to be unsafe or not effective. The following drug products may not be compounded under the exemptions provided by section 503A(a) of the Federal Food, Drug, and Cosmetic Act. Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride is included on this list. /Fenfluramine Hydrochloride/

21 CFR 216.24; U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 26, 2005: http://www.ecfr.gov

HSDB

Schedules of controlled substances are established by section 202 of the Controlled Substances Act (21 U.S.C. 812). Any material, compound, mixture, or preparation which contains any quantity of the following substances, including its salts, isomers (whether optical, position, or geometric), and salts of such isomers, whenever the existence of such salts, isomers, and salts of isomers is possible: Fenfluramine, Schedule IV, DEA Code #: 1670.

21 CFR 1308.14(d); U.S. National Archives and Records Administration's Electronic Code of Federal Regulations. Available from, as of October 26, 2005: http://www.ecfr.gov

HSDB

11.4 Other Safety Information

11.4.1 Special Reports

du Verglas G et al; Clinical Effects of Fenfluramine on Children with Autism: a Review of the Research. J Autism Dev Disord 18 (2): 297-308 (1988). A review of research studies published to date on the effects of fenfluramine on children with autism is presented. The current status of the fenfluramine research on children with autism is assessed. The review analyzed the methodological aspects of the research, the toxicity of fenfluramine, and the relationship between fenfluramine, neurotransmitter activity, cognitive ability, and subsequent behavioral change. The review of published data indicated that fenfluramine had positive effects on the reduction of hyperactivity and stereotypic behaviors in 33% of the subjects. The best responders were children with the highest baseline IQs. The conclusions address the need for appropriate subgrouping of autistic syndromes, which may lead to identification of responders to pharmacological treatments. The need for further study of the possible long-term adverse side effects of flenfluramine is noted. Further experimental research on the effects of fenfluramine on children with autism is endorsed.

HSDB

12 Toxicity

12.1 Toxicological Information

12.1.1 Acute Effects

▶ ChemIDplus

12.1.2 Interactions

Headache, neck stiffness, nausea, and collapse occurred following a single 20 mgdose of fenfluramine hydrochloride in a patient taking a monoamine oxidase inhibitor. In addition, neurologic and circulatory reactions, including hypertensive crises, have been reported in patients who have received sympathomimetic agents concomitantly with monoamine oxidase inhibitors and fatalities have occurred. Fenfluramine is, therefore, contraindicated during or within 14 days following the administration of monoamine oxidase inhibitors. /Fenfluramine hydrochloride/

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

▶ HSDB

Fenfluramine should be used with caution in patients taking CNS depressant drugs since the effects may be additive.

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1771

▶ HSDB

'Fen-phen' refers to the off-label combination of the appetite suppressants fenfluramine and phentermine. The rationale for the fen-phen combination was that the two drugs exerted independent actions on brain satiety mechanisms so that it was possible to use lower doses of each drug and yet retain a common action on suppressing appetite while minimizing adverse drug effects. The focus of the present review is to consider whether fenfluramine and phentermine exert actions that are additive in nature or whether these two drugs exhibit drug-drug synergism. The fen-phen combination results in synergism for the suppression of appetite and body weight, the reduction of brain serotonin levels, pulmonary vasoconstriction and valve disease. Fen-phen synergism may reflect changes in the pharmacokinetics of drug distribution, common actions on

membrane ion currents, or interactions between neuronal release and reuptake mechanisms with MAO-mediated transmitter degradation. The synergism between fenfluramine and phentermine highlights the need to more completely understand the pharmacology and neurochemistry of appetite suppressants prior to use in combination pharmacotherapy for the treatment of obesity.

PMID:10454106
Wellman PJ, Maher TJ; Int J Obes Relat Metab Disord 23 (7): 723-32 (1999)

▶ HSDB

... Prior treatment with diethylcarbamazine was found to potentiate the lethality of fenfluramine, while cyproheptadine pretreatment attenuated fenfluramine's toxic effects. Necropsies, conducted 24 hr after fenfluramine administration, revealed widespread alveolar and pulmonary interstitial hemorrhage in the cyproheptadine pretreated animals. The data suggest that high doses of fenfluramine directly result in pulmonary hypertension, which secondarily induces ischemic cardiac injury.

PMID:2367283
Hunsinger RN, Wright D; Pharmacol Res 22 (3): 371-8 (1990)

▶ HSDB

12.1.3 Toxicity Summary

Agitation and drowsiness, confusion, flushing, tremor (or shivering), fever, sweating, abdominal pain, hyperventilation, and dilated non-reactive pupils seem frequent in fenfluramine overdosage. Reflexes may be either exaggerated or depressed and some patients may have rotary nystagmus. Tachycardia may be present, but blood pressure may be normal or only slightly elevated. Convulsions, coma, and ventricular extrasystoles, culminating in ventricular fibrillation, and cardiac arrest, may occur at higher dosages. Less than 5 mg/kg are toxic to humans. Five-ten mg/kg may produce coma and convulsions. Reported single overdoses have ranged from 300 to 2000 mg; the lowest reported fatal dose was a few hundred mg in a small child, and the highest reported nonfatal dose was 1800 mg in an adult. Most deaths were apparently due to respiratory failure and cardiac arrest. Toxic effects will appear within 30 to 60 minutes and may progress rapidly to potentially fatal complications in 90 to 240 minutes. Symptoms may persist for extended periods depending upon the dose ingested.

▶ DrugBank

IDENTIFICATION: Fenfluramine hydrochloride is a centrally acting amphetamine antiobesity assent. HUMAN EXPOSURE: Main risks and target organs: Acute central nervous system stimulation, cardiotoxicity causing tachycardia, arrhythmias, hypertension and cardiovascular collapse. High risk of dependency and abuse. Summary of clinical effects: Cardiovascular: Palpitation, chest pain, tachycardia, arrhythmias and hypertension are common; cardiovascular collapse can occur in severe poisoning. Myocardial ischaemia, infarction and ventricular dysfunction are described. Central Nervous System (CNS): Stimulation of CNS, tremor, restlessness, agitation, insomnia, increased motor activity, headache, convulsions, coma and hyperreflexia are described. Stroke and cerebral vasculitis have been observed. Gastrointestinal: Vomiting, diarrhea and cramps may occur. Acute transient ischemic colitis has occurred with chronic methamphetamine abuse. Genitourinary: Increased bladder sphincter tone may cause dysuria, hesitancy and acute urinary retention. Renal failure can occur secondary to dehydration or rhabdomyolysis. Renal ischemia may be noted. Dermatologic: Skin is usually pale and diaphoretic, but mucous membranes appear dry. Endocrine: Transient hyperthyroxinemia may be noted. Metabolism: Increased metabolic and muscular activity may result in hyperventilation and hyperthermia. Weight loss is common with chronic use. Fluid/Electrolyte: Hypo- and hyperkalemia have been reported. Dehydration is common. Musculoskeletal: Fasciculations and rigidity may be noted. Rhabdomyolysis is an important consequence of severe amphetamine poisoning. Psychiatric: Agitation, confusion, mood elevation, increased wakefulness, talkativeness, irritability and panic attacks are typical. Chronic abuse can cause delusions and paranoia. A withdrawal syndrome occurs after abrupt cessation following chronic use. Contraindications: Anorexia, insomnia, psychopathic personality disorders, suicidal tendencies, Gilles de la Tourette syndrome and other disorders, hyperthyroidism, narrow angle glaucoma, diabetes mellitis and cardiovascular diseases such as angina, hypertension and arrythmias. Routes of exposure: Oral: Readily absorbed from the gastro-intestinal tract and buccal mucosa. It is resistant to metabolism by monoamine oxidase. Inhalation: Amphetamine is rapidly absorbed by inhalation and is

abused by this route. Parenteral: Frequent route of entry in abuse situations. Absorption by route of exposure: Amphetamine is rapidly absorbed after oral ingestion. Peak plasma levels occur within 1 to 3 hours, varying with the degree of physical activity and the amount of food in the stomach. Absorption is usually complete by 4 to 6 hours. Sustained release preparations are available as resin-bound, rather than soluble, salts. These compounds display reduced peak blood levels compared with standard amphetamine preparations, but total amount absorbed and time to peak levels remain similar. Distribution by route of exposure: Amphetamines are concentrated in the kidney, lungs, cerebrospinal fluid and brain. They are highly lipid soluble and readily cross the blood-brain barrier. Protein binding and volume of distribution varies widely, but the average volume of distribution is 5 L/kg body weight. Biological half-life by route of exposure: Under normal conditions, about 30% of amphetamine is excreted unchanged in the urine but this excretion is highly variable and is dependent on urinary pH. When the urinary pH is acidic (pH 5.5 to 6.0), elimination is predominantly by urinary excretion with approximately 60% of a dose of amphetamine being excreted unchanged by the kidney within 48 hours. When the urinary pH is alkaline (pH 7.5 to 8.0), elimination is predominantly by deamination (less than 7% excreted unchanged in the urine); the half-life ranging from 16 to 31 hours. Metabolism: The major metabolic pathway for amphetamine involves deamination by cytochrome P450 to para-hydroxyamphetamine and phenylacetone; this latter compound is subsequently oxidized to benzoic acid and excreted as glucuronide or glycine (hippuric acid) conjugate. Smaller amounts of amphetamine are converted to norephedrine by oxidation. Hydroxylation produces an active metabolite, O-hyroxynorephedrine, which acts as a false neurotransmitter and may account for some drug effect, especially in chronic users. Elimination and excretion: Normally 5 to 30% of a therapeutic dose of amphetamine is excreted unchanged in the urine by 24 hours, but the actual amount of urinary excretion and metabolism is highly pH dependent. Mode of action: Toxicodynamics: Amphetamine appears to exert most or all of its effect in the CNS by causing release of biogenic amines, especially norepinephrine and dopamine, from storage sites in nerve terminals. It may also slow down catecholamine metabolism by inhibiting monoamine oxidase. Adults: The toxic dose varies considerably due to individual variations and the development of tolerance. Children: Children appear to be more susceptible than adults and are less likely to have developed tolerance. Teratogenicity: The use of amphetamine for medical indications does not pose a significant risk to the fetus for congenital anomalies. Amphetamines generally do not appear to be human teratogens. Mild withdrawal symptoms may be observed in the newborn, but the few studies of infant follow-up have not shown long-term sequelae. Illicit maternal use or abuse of amphetamine presents a significant risk to the fetus and newborn, including intrauterine growth retardation, premature delivery and the potential for increased maternal, fetal and neonatal morbidity. Cerebral injuries occurring in newborns exposed in utero appear to be directly related to the vasoconstrictive properties of amphetamines. Sixty-five children were followed whose mothers were addicted to amphetamine during pregnancy, at least during the first trimester. Intelligence, psychological function, growth, and physical health were all within the normal range at eight years, but those children exposed throughout pregnancy tended to be more aggressive. Interactions: Acetazolamide: administration may increase serum concentration of amphetamine. Alcohol: may increase serum concentration of amphetamine. Ascorbic acid: lowering urinary pH, may enhance amphetamine excretion Furazolidone: amphetamines may induce a hypertensive response in patients taking furazolidone. Guanethidine: amphetamine inhibits the antihypertensive response to guanethidine. Haloperidol: limited evidence indicates that haloperidol may inhibit the effects of amphetamine but the clinical importance of this interaction is not established. Lithium carbonate: isolated case reports indicate that lithium may inhibit the effects of amphetamine. Monoamine oxidase inhibitor: severe hypertensive reactions have followed the administration of amphetamines to patients taking monoamine oxidase inhibitors. Noradrenaline: amphetamine abuse may enhance the pressor response to noradrenaline. Phenothiazines: amphetamine may inhibit the antipsychotic effect of phenothiazines, and phenothiazines may inhibit the anorectic effect of amphetamines. Sodium bicarbonate: large doses of sodium bicarbonate inhibit the elimination of amphetamine, thus increasing the amphetamine effect. Tricyclic antidepressants - theoretically increases the effect of amphetamine, but clinical evidence is lacking. Clinical effects: Acute poisoning: Ingestion: Effects are most marked on the central nervous system, cardiovascular system, and muscles. The triad of hyperactivity, hyperpyrexia, and hypertension is characteristic of acute amphetamine overdosage. Agitation, confusion, headache, delirium, and hallucination, can be followed by coma, intracranial hemorrhage, stroke, and death. Chest pain, palpitation, hypertension, tachycardia, atrial and ventricular arrhythmia, and myocardial infarction can occur. Muscle contraction, bruxism (jaw-grinding), trismus (jaw clenching), fasciculation, rhabdomyolysis, are seen leading to renal failure; and flushing, sweating, and hyperpyrexia can all occur. Hyperpyrexia can cause disseminated intravascular coagulation. Inhalation: The clinical effects are similar to those after ingestion, but occur more rapidly. Parenteral exposure: Intravenous injection is a common mode of administration of amphetamine by abusers. Other clinical effects are similar to those observed after ingestion, but occur

more rapidly. Ingestion: Tolerance to the euphoric effects and CNS stimulation induced by amphetamine develops rapidly, leading abusers to use larger and larger amounts to attain and sustain the desired affect. Habitual use or chronic abuse usually results in toxic psychosis classically characterised by paranoia, delusions and hallucinations, which are usually visual, tactile or olfactory in nature, in contrast to the typical auditory hallucinations of schizophrenia. The individual may act on the delusions, resulting in bizarre violent behavior, hostility and aggression, sometimes leading to suicidal or homicidal actions. Dyskinesia, compulsive behaviour and impaired performance are common in chronic abusers. The chronic abuser presents as a restless, garrulous, tremulous individual who is suspicious and anxious. Course, prognosis, cause of death: Symptoms and signs give a clinical guide to the severity of intoxication as follows: Mild toxicity: restlessness, irritability, insomnia, tremor, hyperreflexia, sweating, dilated pupils, flushing. Moderate toxicity: hyperactivity, confusion, hypertension, tachypnea, tachycardia, mild fever, sweating. Severe toxicity: delirium, mania, self-injury, marked hypertension, tachycardia, arrhythmia, hyperpyrexia, convulsion, coma, circulatory collapse. Death can be due to intracranial hemorrhage, acute heart failure or arrhythmia, hyperpyrexia, rhabdomyolysis and consequent hyperkalaemia or renal failure, and to violence related to the psychiatric effects. Systematic description of clinical effects: Cardiovascular: Cardiovascular symptoms of acute poisoning include palpitation and chest pain. Tachycardia and hypertension are common. Severe poisoning can cause acute myocardial ischemia, myocardial infarction and left ventricular failure. Chronic oral amphetamine abuse can cause a chronic cardiomyopathy; an acute cardiomyopathy has also been described. Hypertensive stroke is a well-recognized complication of amphetamine poisoning. Intra-arterial injection of amphetamine can cause severe burning pain, vasospasm, and gangrene. Respiratory: Pulmonary fibrosis, right ventricular hypertrophy and pulmonary hypertension are frequently found at post-mortem examination. Pulmonary function tests usually are normal except for the carbon monoxide diffusing capacity. Respiratory complications are sometimes caused by fillers or adulterants used in injections by chronic users. These can cause multiple microemboli to the lung, which can lead to restrictive lung disease. Pneumomediastinum has been reported after amphetamine inhalation. Neurological: Central nervous system (CNS): Main symptoms include agitation, confusion, delirium, hallucinations, dizziness, dyskinesia, hyperactivity, muscle fasciculation and rigidity, rigors, tics, tremors, seizures and coma. Both occlusive and hemorrhagic strokes have been reported after abuse of amphetamines. Patients with underlying arteriovenous malformations may be at particular risk. Stroke can occur after oral, intravenous, or nasal administration. Severe headache beginning within minutes of ingestion of amphetamine is usually the first symptom. In more than half the cases, hypertension which is sometimes extreme, accompanies other symptoms. A Cerebral vasculitis has also been observed. Dystonia and dyskinesia can occur, even with therapeutic dosages. Psychiatric effects, particularly euphoria and excitement, are the motives for abuse. Paranoia and a psychiatric syndrome indistinguishable from schizophrenia are sequelae of chronic use. Autonomic nervous system: Stimulation of alpha-adrenergic receptors produces mydriasis, increased metabolic rate, diaphoresis, increased sphincter tone, peripheral vasoconstriction and decreased gastrointestinal motility. Stimulation of ß-adrenergic receptors produces increased heart rate and contractility, increased automaticity and dilatation of bronchioles. Skeletal and smooth muscle: Myalgia, muscle tenderness, muscle contractions, and rhabdomyolysis, leading to fever, circulatory collapse, and myoglobinuric renal failure, can occur with amphetamines. Gastrointestinal: Most common symptoms are nausea, vomiting, diarrhea, and abdominal cramps. Anorexia may be severe. Epigastric pain and hematemesis have been described after intravenous amphetamine use. A case of ischemic colitis with normal mesenteric arteriography in a patient taking dexamphetamine has been described. Hepatic: Hepatitis and fatal acute hepatic necrosis have been described. Urinary: Renal: Renal failure, secondary to dehydration or rhabdomyolysis may be observed. Other: Spontaneous rupture of the bladder has been described in a young woman who took alcohol and an amphetamine-containing diet tablet. Endocrine and reproductive systems: Transient hyperthyroxinemia may result from heavy amphetamine use. Dermatological: Skin is usually pale and diaphoretic, but mucous membranes appear dry. Chronic users may display skin lesion, abscesses, ulcers, cellulitis or necrotising angiitis due to physical insult to skin, or dermatologic signs of dietary deficiencies, cheilosis and purpura. Eye, ear, nose, throat: local effects: Mydriasis may be noted. Diffuse hair loss may be noted. Chronic users may display signs of dietary deficiencies. Hematological: Disseminated intravascular coagulation is an important consequence of severe poisoning. Idiopathic thrombocytopenic purpura may occur. Metabolic: Fluid and electrolyte disturbance: Increase metabolic and muscular activity may result in dehydration. /Fenfluramine hydrochloride/

International Programme on Chemical Safety; Poisons Information Monograph: Fenfluramine Hydrochloride (PIM 938) (1998) Available from, as of May 19, 2005: http://www.inchem.org/pages/pims.html

▸ HSDB

12.1.4 Antidote and Emergency Treatment

Treatment: Acute overdose can be rapidly fatal. The treatment is primarily supportive. All patients should have an adequate airway established, IV access, and cardiac monitoring.

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 875

HSDB

Decontamination: Induction of emesis is contraindicated due to the rapid onset of symptoms and possible loss of airway control. A single dose of activated charcoal should be administered if the patient presents within a couple of hours of exposure. Whole bowel irrigation may be of benefit for ingestion of sustained release tablets although its efficacy has not been studied.

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 875

HSDB

Antidotes: Cyproheptadine, a serotonin receptor antagonist, has been recommended as adjunct therapy for severe serotonin syndrome. ...

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 875

HSDB

Supportive Care: Benzodiazepine are indicated for muscle rigidity, seizure activity, or agitation ... . Hypotension should be managed with IV crystalloid fluid bolus ... followed by vasopressors as needed.

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 875

HSDB

Maintain open airway and assist ventilation if necessary. Treat agitation, seizures, coma, and hypothermia if they occur. Continually monitor temperature, other vital signs, and the ECG for a minimum of 6 hours. Hypertension is best treated with parenteral vasodilator such as phentolamine or nitroprusside. Treat tachyarrhythmias with propranolol or esmolol. Treat arterial vasospasm /with/ nitroglycerin sublingually ... /or/ iv. Intracoronary artery nitroglycerin may be required if there is no response to intravenous infusion. Also consider using a calcium antagonist. /Amphetamines/

Olson, K.R. (Ed.); Poisoning & Drug Overdose. 4th ed. Lange Medical Books/McGraw-Hill. New York, N.Y. 2004., p. 74

HSDB

Do not induce vomiting because of the risk of abrupt onset of seizures. Administer activated charcoal. Gastric emptying is not necessary if activated charcoal can be given promptly. Dialysis and hemoperfusion are not effective. Repeat dose charcoal has not been studied... /Amphetamines/

Olson, K.R. (Ed.); Poisoning & Drug Overdose. 4th ed. Lange Medical Books/McGraw-Hill. New York, N.Y. 2004., p. 74

HSDB

There is no specific antidote for overdosage with appetite suppressants; treatment is symptomatic and supportive. To decrease absorption; induction of emesis and/or use of gastric lavage followed by the administration of activated charcoal. To enhance elimination; Acidification of urine and force diuresis, with serum electrolyte evaluations during prolonged diuresis. /Appetite Suppressants, Sympathomimetic/

Thomson.Micromedex. Drug Information for the Health Care Professional. 25th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2005., p. 441

HSDB

Specific treatment /includes/ barbiturate sedatives or diazepam sometimes used to control excessive CNS stimulation. Intravenous diazepam to control seizures; phenytoin to control seizures that are refractory to diazepam. When hyperthermia and rhabdomyolysis are present, curarization may be required. Intravenous phentolamine or nitrates, if necessary, to control acute, severe hypertension. Intravenous lidocaine for cardiac arrhythmias. Beta- adrenergic blocking agent for control of tachycardia. /Appetite Suppressants, Sympathomimetic/

Thomson.Micromedex. Drug Information for the Health Care Professional. 25th ed. Volume 1. Plus Updates. Content Reviewed by the United States Pharmacopeial Convention, Inc. Greenwood Village, CO. 2005., p. 441

HSDB

12.1.5 Human Toxicity Excerpts

/HUMAN EXPOSURE STUDIES/ Not all the risk factors for primary pulmonary hypertension (PPH) are known. Appetite suppressants, including fenfluramine derivatives, are strongly suspected aetiological agents. In a 5 year retrospective study fenfluramine use was evaluated among patients referred to a medical centre specialising in the management of PPH. Fifteen (20%) of 73 patients with PPH had used fenfluramine: all of them were women and in 10 (67%) there was a close temporal relation between fenfluramine use and the development of exertional dyspnoea. Initial right heart catheterisation in the 15 women showed severe resting pulmonary hypertension (mean (SD)) with pulmonary artery pressure (PAP) 57 (9) mm Hg, cardiac index 2.1 (0.5) l/min/sq M, and pulmonary vascular resistance (PVR) 29 (10) U/sq m. Short-term epoprostenol infusion produced a significant vasodilator response in 10 patients (mean fall in PVR 24 (15%) compared with control values). Three fenfluramine users with PPH showed spontaneous clinical and haemodynamic improvement 3, 6 and 12 months after drug withdrawal but there was no significant difference in overall survival (transplant recipients excluded) between fenfluramine users and controls. Histological examination of lung tissue from five women who had used fenfluramine and 22 controls, with PPH showed features typical of advanced plexogenic pulmonary arteriopathy in all. These results do not accord with earlier reports that PPH associated with fenfluramine is less severe and has a better outcome. Fenfluramine may be one aetiological agent that can precipitate or hasten the development of PPH.

PMID:8280518
Full text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1025385
Brenot F et al; Br Heart J 70 (6): 537-41 (1993)

HSDB

/HUMAN EXPOSURE STUDIES/ Three subjects given 240 mg of fenfluramine experienced brief but vivid hallucinogenic episodes characterized by olfactory, visual, & somatic hallucinations, abrupt polar changes in mood, time distortion, fleeting paranoia, & sexual ideation.

PMID:1102234
Griffth JD et al; Clin Pharmacol Ther 18: 563-70 (1975)

HSDB

/HUMAN EXPOSURE STUDIES/ Fenfluramine doses of less than 5 mg/kg are toxic, and doses of 5-10 mg/kg may produce coma and seizures. ... Single overdoses reported have ranged from 300 mg to 2 g. The lowest reported fatal dose of fenfluramine hydrochloride was 400 mg in a small child and the highest reported nonfatal dose was 1.8 g in an adult.

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1771

HSDB

/SIGNS AND SYMPTOMS/ Emotional instability, cognitive deficits, and depression were reported in 27 patients taking fenfluramine and dexfenfluramine chronically. Psychosis has been reported after use of dexfenfluramine for 2 months. Headache, diarrhea, dizziness, dry mouth, impotence, palpitations , anxiety, insomnia, irritability, lethargy, and CNS excitation at higher doses have been reported with therapeutic use.

Dart, R.C. (ed). Medical Toxicology. Third Edition, Lippincott Williams & Wilkins. Philadelphia, PA. 2004., p. 875

HSDB

For more Human Toxicity Excerpts (Complete) data for FENFLURAMINE (19 total), please visit the HSDB record page.

HSDB

12.1.6 Non-Human Toxicity Excerpts

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ ... Negative teratolgic testing /was reported/ in rats, rabbits and mice. Doses of up to 45 mg per kg /of fenfluramine/ were given subcutaneously to rats on days 5 through 14 of gestation. Postnatal studies of rats whose mothers received 20 mg per kg daily during most of gestation were reported to be different from controls. Locomotor tests (pivoting) were the most altered. Brain weight, but not DNA, was significantly reduced in the pups at 70 days of postnatal life.

Shepard, T.H. Catalog of Teratogenic Agents. 5th ed. Baltimore, MD: The Johns Hopkins University Press, 1986., p. 256

HSDB

/LABORATORY ANIMALS: Developmental or Reproductive Toxicity/ Studies in rats showed decreases in the rate of conception and survival rate at weaning and some potential teratogenicity; however, no adverse effects were reported in reproduction studies in other species (rabbits, monkeys, mice, and chickens).

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1770

HSDB

/LABORATORY ANIMALS: Acute Exposure/ Fenfluramine is a potent serotonin releasing drug used primarily as an anorectic agent. The symptomatology of its acute lethality has been well documented in animal models such as the rat. A very prominent feature of this lethality profile is hypoxia, as demonstrated by the onset of severe cyanosis just prior to death. It is not clear in the literature whether this hypoxia is the result of a direct pulmonary effect or is secondary to cardiac injury. To further characterize this aspect of fenfluramine's toxicity, respiratory and electrocardiographic measurements were taken in anesthetized rats subjected to high doses of fenfluramine (129.6 mg/kg, ip). Death occurred in these animals within 15 min of drug administration, apparently as the result of abrupt respiratory cessation, followed by cardiac ischemia. No significant gross or histopathological lesions were evident in these animals.

PMID:2367283
Hunsinger RN, Wright D; Pharmacol Res 22 (3): 371-8 (1990)

HSDB

/GENOTOXICITY/ Fenfluramine, an amphetamine derivative used in the treatment of obesity, has been evaluated in vivo in the bone marrow cells of Swiss albino mice using two cytogenetic endpoints for assessing its genotoxic and clastogenic potentials. Concentrations of 0.75, 1.5, 3.0, and 5.0 mg/kg b.w. were administered orally for the study of sister chromatid exchange frequencies and chromosome aberrations (CA). SCE frequencies showed a positive dose response; 1.5 mg/kg being the minimum effective concentration. Fen caused a prolongation of cell cycle at all concentrations. Except for the minimum therapeutic dose (0.75 mg), all other doses (1.5, 3.0, and 5.0 mg) showed a significant increase in the percentage of damaged cells over that of the vehicle control. The degree of clastogenicity was directly proportional to the dosage used and inversely related with the duration of treatment. A gradual reduction of the clastogenic potential was observed after 12 and 24 hr of exposure, indicating that the maximum effect occurs at the middle or late synthetic phase of the cell cycle. This study, probably the first detailed screening of the drug for its genotoxicity, shows that Fen is moderately clastogenic and a DNA damaging agent in vivo.

PMID:1600959

Agarwal K et al; Environ Mol Mutagen 19 (4): 323-6 (1992)

HSDB

12.1.7 Populations at Special Risk

Clinical studies of dexfenfluramine did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients. Because geriatric patients generally are more sensitive to drugs that affect the CNS, dexfenfluramine should be used with caution in these patients. The greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly should also be considered. /Dexfenfluramine/

McEvoy, G.K. (ed.). American Hospital Formulary Service - Drug Information 97. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 1997 (Plus Supplements)., p. 1784

HSDB

12.2 Ecological Information

12.2.1 Environmental Fate/Exposure Summary

Fenfluramine's former production and use as a pharmaceutical agent for the treatment of obesity may result in its release to the environment through various waste streams. If released to air, an estimated vapor pressure of 4.1X10-2 mm Hg at 25 °C indicates fenfluramine will exist solely as a vapor in the atmosphere. Vapor-phase fenfluramine will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 4 hours. Fenfluramine does not contain chromophores that absorb at wavelengths >290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight. If released to soil, fenfluramine is expected to have low mobility based upon an estimated Koc of 1,600. The pKa of fenfluramine is 9.6, indicating that this compound will partially exist in the cation form in the environment and cations generally adsorb more strongly to organic carbon and clay than their neutral counterparts. Volatilization from moist soil surfaces is expected to be an important fate process based upon an estimated Henry's Law constant of 2.7X10-5 atm-cu m/mole. Biodegradation data were not available for fenfluramine. If released into water, fenfluramine is not expected to adsorb to suspended solids and sediment based upon the estimated Koc. Volatilization from water surfaces is expected to be an important fate process based upon this compound's estimated Henry's Law constant. Estimated volatilization half-lives for a model river and model lake are 2 days and 20 days, respectively. An estimated BCF of 80 suggests the potential for bioconcentration in aquatic organisms is moderate. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions. Occupational exposure to fenfluramine may have occurred through dermal contact with this compound at workplaces where fenfluramine was produced or used. Exposure to fenfluramine among the general population may have been limited to those administered the drug. (SRC)

HSDB

12.2.2 Artificial Pollution Sources

Fenfluramine's former production and use as a pharmaceutical agent for the treatment of obesity(1) may result in its release to the environment through various waste streams(SRC).

(1) FDA: Center for Drug Evaluation and Research; Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux). Available at http://www.fda.gov/cder/news/phen/fenphenqa2.htm as of March 30, 2006.

HSDB

12.2.3 Environmental Fate

TERRESTRIAL FATE: Based on a classification scheme, an estimated Koc value of 1,600(SRC), determined from a log Kow of 3.36(2) and a regression-derived equation(3), indicates that fenfluramine is expected to have low mobility in soil(SRC). The pKa of fenfluramine is 9.6(4), indicating that this compound will partially exist in the cation form in the environment and cations generally adsorb more strongly to organic carbon and clay than their neutral counterparts(5). Volatilization of fenfluramine from moist soil surfaces is expected to be an important fate process(SRC) given an estimated Henry's Law constant of 2.7X10-5 atm-cu m/mole(SRC), using a fragment constant estimation method(6). Fenfluramine is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 4.1X10-2 mm Hg(SRC), determined from a fragment constant method(7). Biodegradation data were not available(SRC, 2005).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Sangster, J; Log Kow Data Bank. Montreal, Quebec, Canada: Sangster Res. Lab. (1993) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 4-9 (1990) (4) Hilal SH et al; pp. 291-353 in Quantitative Treatments of Solute/Solvent Interactions: Theoretical and Computational Chemistry Vol. 1 NY, NY: Elsevier (1994). SPARC pkA/property server available at http://ibmlc2.chem.uga.edu/sparc/ as of October 14, 2005. (5) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds, Boca Raton, FL: Lewis Publ (2000) (6) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (7) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)

HSDB

AQUATIC FATE: Based on a classification scheme(1), an estimated Koc value of 1,600(SRC), determined from a log Kow of 3.36(2) and a regression-derived equation(3), indicates that fenfluramine is not expected to adsorb to suspended solids and sediment(SRC). The pKa of fenfluramine is 9.6(4), indicating that this compound will partially exist in the cation form in the environment and cations generally adsorb more strongly to organic carbon and clay than their neutral counterparts and do not volatilize(5). Volatilization of the unionized species from water surfaces is expected(3) based upon an estimated Henry's Law constant of 2.7X10-5 atm-cu m/mole(SRC), developed using a fragment constant estimation method(4). Using this Henry's Law constant and an estimation method(6), volatilization half-lives for a model river and model lake are 2 days and 20 days, respectively(SRC). According to a classification scheme(7), an estimated BCF of 80(SRC), from its log Kow(2) and a regression-derived equation(8), suggests the potential for bioconcentration in aquatic organisms is moderate(SRC). Biodegradation data were not available(SRC, 2005).

(1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Sangster J; Log Kow Data Bank. Montreal, Quebec, Canada: Sangster Res. Lab. (1993) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 4-9, 15-1 to 15-29 (1990) (4) Hilal SH et al; pp. 291-353 in Quantitative Treatments of Solute/Solvent Interactions: Theoretical and Computational Chemistry Vol. 1 NY, NY: Elsevier (1994). SPARC pkA/property server available at http://ibmlc2.chem.uga.edu/sparc/ as of October 14, 2005. (5) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds, Boca Raton, FL: Lewis Publ (2000) (6) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (7) Franke C et al; Chemosphere 29: 1501-14 (1994) (8) Meylan WM et al; Environ Toxicol Chem 18: 664-72 (1999)

HSDB

ATMOSPHERIC FATE: According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere(1), fenfluramine, which has an estimated vapor pressure of 4.1X10-2 mm Hg at 25 °C(SRC), determined from a fragment constant method(2), is expected to exist solely as a vapor in the ambient atmosphere. Vapor-phase fenfluramine is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals(SRC); the half-life for this reaction in air is estimated to be 4 hours(SRC), calculated from its rate constant of 3.3X10-11 cu cm/molecule-sec at 25 °C (SRC) that was derived using a structure estimation method(3). Fenfluramine does not contain chromophores that absorb at wavelengths >290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight(SRC).

(1) Bidleman TF; Environ Sci Technol 22: 361-367 (1988) (2) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985) (3) Meylan WM, Howard PH; Chemosphere 26: 2293-99 (1993)

HSDB

12.2.4 Environmental Abiotic Degradation

The rate constant for the vapor-phase reaction of fenfluramine with photochemically-produced hydroxyl radicals has been

estimated as 3.3X10-11 cu cm/molecule-sec at 25 °C(SRC) using a structure estimation method(1). This corresponds to an atmospheric half-life of about 4 hours at an atmospheric concentration of 5X10+5 hydroxyl radicals per cu cm(1). Fenfluramine is not expected to undergo hydrolysis in the environment due to the lack of functional groups that hydrolyze under environmental conditions(2). Fenfluramine does not contain chromophores that absorb at wavelengths >290 nm and therefore is not expected to be susceptible to direct photolysis by sunlight(SRC).

(1) Meylan WM, Howard PH; Chemosphere 26: 2293-99 (1993) (2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 7-4, 7-5 (1990)

▸ HSDB

12.2.5 Environmental Bioconcentration

An estimated BCF of 80 was calculated for fenfluramine(SRC), using a log Kow of 3.36(1) and a regression-derived equation(2). According to a classification scheme(3), this BCF suggests the potential for bioconcentration in aquatic organisms is moderate(SRC), provided the compound is not metabolized by the organism(SRC).

(1) Sangster J; Log Kow Data Bank. Montreal, Quebec, Canada: Sangster Res. Lab. (1993) (2) Meylan WM et al; Environ Toxicol Chem 18: 664-72 (1999) (3) Franke C et al; Chemosphere 29: 1501-14 (1994)

▸ HSDB

12.2.6 Soil Adsorption/Mobility

The Koc of fenfluramine is estimated as 1,600(SRC), using a log Kow of 3.36(1) and a regression-derived equation(2). According to a classification scheme(3), this estimated Koc value suggests that fenfluramine is expected to have low mobility in soil. The pKa of fenfluramine is 9.6(4), indicating that this compound will partially exist in the cation form in the environment and cations generally adsorb more strongly to organic carbon and clay than their neutral counterparts(5).

(1) Sangster J; Log Kow Data Bank. Montreal, Quebec, Canada: Sangster Res. Lab. (1993)(2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 4-9 (1990) (3) Swann RL et al; Res Rev 85: 17-28 (1983) (4) (1) Swann RL et al; Res Rev 85: 17-28 (1983) (2) Sangster J; Log Kow Data Bank. Montreal, Quebec, Canada: Sangster Res. Lab. (1993) (3) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 4-9, 15-1 to 15-29 (1990) (4) Hilal SH et al; pp. 291-353 in Quantitative Treatments of Solute/Solvent Interactions: Theoretical and Computational Chemistry Vol. 1 NY, NY: Elsevier (1994). SPARC pKa/property server available at http://ibmlc2.chem.uga.edu/sparc/ as of October 14, 2005. (5) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds, Boca Raton, FL: Lewis Publ (2000) (6) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (7) Franke C et al; Chemosphere 29: 1501-14 (1994) (8) Meylan WM et al; Environ Toxicol Chem 18: 664-72 (1999) (5) Doucette WJ; pp. 141-188 in Handbook of Property Estimation Methods for Chemicals. Boethling RS, Mackay D, eds, Boca Raton, FL: Lewis Publ (2000)

▸ HSDB

12.2.7 Volatilization from Water/Soil

The Henry's Law constant for fenfluramine is estimated as 2.7X10-5 atm-cu m/mole(SRC) using a fragment constant estimation method(1). This Henry's Law constant indicates that fenfluramine is expected to volatilize from water surfaces(2). Based on this Henry's Law constant, the volatilization half-life from a model river (1 m deep, flowing 1 m/sec, wind velocity of 3 m/sec)(2) is estimated as 2 days(SRC). The volatilization half-life from a model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec)(2) is estimated as 20 days(SRC). Fenfluramine's Henry's Law constant indicates that volatilization from moist soil surfaces may occur(SRC). Fenfluramine is not expected to volatilize from dry soil surfaces(SRC) based upon an estimated vapor pressure of 4.1X10-2 mm Hg(SRC), determined from a fragment constant method(3).

(1) Meylan WM, Howard PH; Environ Toxicol Chem 10: 1283-93 (1991) (2) Lyman WJ et al; Handbook of Chemical Property Estimation Methods. Washington, DC: Amer Chem Soc pp. 15-1 to 15-29 (1990) (3) Lyman WJ; p. 31 in Environmental Exposure From Chemicals Vol I, Neely WB, Blau GE, eds, Boca Raton, FL: CRC Press (1985)

▸ HSDB

12.2.8 Environmental Water Concentrations

While data on fenfluramine were not available (SRC, 2005), the literature suggests that some pharmaceutically active compounds originating from human and veterinary therapy are not eliminated completely in municipal sewage treatment plants and are therefore discharged into receiving waters(1). Wastewater treatment processes often were not designed to remove them from the effluent(2). Another concern is that selected organic waste compounds may be degrading to new and more persistent compounds that may be released instead of or in addition to the parent compound(2). Studies have indicated that several polar pharmaceutically active compounds can leach through subsoils into aquifers(1).

(1) Heberer T; Tox Lett 131: 5-17 (2002) (2) Koplin DW et al; Environ Sci Toxicol 36: 1202-211 (2002)

HSDB

12.2.9 Other Environmental Concentrations

Specific data were not available on the environmental concentrations of fenfluramine; however, the compound has been selected for monitoring due to constant discharge into the environment through it's use as a pharmaceutical agent(1).

(1) Daughton CG, Ternes TA; Environ Hlth Perspect 107: 907-938 (1999)

HSDB

12.2.10 Probable Routes of Human Exposure

Occupational exposure to fenfluramine may have occurred through dermal contact with this compound at workplaces where fenfluramine was produced or used. Exposure to fenfluramine among the general population may have been limited to those administered the drug as a treatment for obesity. (SRC)

HSDB

13 Literature

13.1 NLM Curated PubMed Citations

PubChem

13.2 Springer Nature References

Springer Nature

13.3 Thieme References

Thieme Chemistry

13.4 Depositor Provided PubMed Citations

PubChem

13.5 Synthesis References

Vincenzo Cannata, Barbara Galbiati, Angelo Spreafico, "Process for manufacturing 1-(3-trifluoromethyl)-phenyl-propan-2-one intermediate in the synthesis of the fenfluramine." U.S. Patent US5811586, issued August, 1965.

DrugBank

13.6 General References

Roth BL: Drugs and valvular heart disease. N Engl J Med. 2007 Jan 4;356(1):6-9. [PMID:17202450]

- DrugBank

13.7 Chemical Co-Occurrences in Literature

- PubChem

13.8 Chemical-Gene Co-Occurrences in Literature

- PubChem

13.9 Chemical-Disease Co-Occurrences in Literature

PubChem

14 Patents

14.1 Depositor-Supplied Patent Identifiers

PubChem

Link to all deposited patent identifiers

PubChem

14.2 WIPO PATENTSCOPE

Patents are available for this chemical structure:

https://patentscope.wipo.int/search/en/result.jsf?inchikey=DBGIVFWFUFKIQN-UHFFFAOYSA-N

PATENTSCOPE (WIPO)

15 Biomolecular Interactions and Pathways

15.1 Drug-Gene Interactions

▸ Drug Gene Interaction database (DGIdb)

15.2 DrugBank Interactions

Showing 1 of 5 View More

Target	Sodium-dependent serotonin transporter
Action	inhibitor
PubChem Protein Target	P31645
PubChem Gene Target	SLC6A4
General Function	Serotonin:sodium symporter activity
Specific Function	Serotonin transporter whose primary function in the central nervous system involves the regulation of serotonergic signaling via transport of serotonin molecules from the synaptic cleft back into the pre-synaptic terminal for re-utilization. Plays a key role in mediating regulation of the availability of serotonin to other receptors of serotonergic systems. Terminates the action of serotonin and recycles it in a sodium-dependent manner.
Interaction References	1. Rothman RB, Zolkowska D, Baumann MH: Serotonin (5-HT) transporter ligands affect plasma 5-HT in rats. Ann N Y Acad Sci. 2008 Oct;1139:268-84. doi: 10.1196/annals.1432.042. [PMID:18991872] 2. Cosgrove KP, Staley JK, Baldwin RM, Bois F, Plisson C, Al-Tikriti MS, Seibyl JP, Goodman MM, Tamagnan GD: SPECT imaging with the serotonin transporter radiotracer [123I]p ZIENT in nonhuman primate brain. Nucl Med Biol. 2010 Jul;37(5):587-91. doi: 10.1016/j.nucmedbio.2010.03.007. Epub 2010 May 6. [PMID:20610163] 3. Xie T, Tong L, McLane MW, Hatzidimitriou G, Yuan J, McCann U, Ricaurte G: Loss of serotonin transporter protein after MDMA and other ring-substituted amphetamines. Neuropsychopharmacology. 2006 Dec;31(12):2639-51. Epub 2006 Jan 25. [PMID:16452989] 4. Johnson GJ, Leis LA, Dunlop PC, Weir EK: The effect of the anorectic agent, d-fenfluramine, and its primary metabolite, d-norfenfluramine, on intact human platelet serotonin uptake and efflux. J Thromb Haemost. 2003 Dec;1(12):2663-8. [PMID:14675103] 5. Rothman RB, Jayanthi S, Wang X, Dersch CM, Cadet JL, Prisinzano T, Rice KC, Baumann MH: High-dose fenfluramine administration decreases serotonin transporter binding, but not serotonin

	transporter protein levels, in rat forebrain. Synapse. 2003 Dec 1;50(3):233-9. [PMID:14515341]

▶ DrugBank

16 Biological Test Results

16.1 BioAssay Results

PubChem

17 Classification

17.1 Ontologies

17.1.1 MeSH Tree

▶ MeSH

17.1.2 ChEBI Ontology

▶ ChEBI

17.1.3 KEGG: ATC

KEGG

17.1.4 KEGG: Target-based Classification of Drugs

KEGG

17.1.5 KEGG: Drug Classes

KEGG

17.1.6 WHO ATC Classification System

WHO ATC

17.1.7 WIPO IPC

- WIPO

17.1.8 ChemIDplus

- ChemIDplus

17.1.9 Guide to PHARMACOLOGY Target Classification

- IUPHAR/BPS Guide to PHARMACOLOGY

17.1.10 UN GHS Classification

▶ UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

17.1.11 EPA CPDat Classification

▶ EPA Chemical and Products Database (CPDat)

18 Information Sources

FILTER BY SOURCE ALL SOURCES

1. ## ChEBI

Fenfluramine
http://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:5000

ChEBI Ontology
http://www.ebi.ac.uk/chebi/userManualForward.do#ChEBI%20Ontology

2. ## DrugBank

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> https://www.drugbank.ca/legal/terms_of_use

Fenfluramine
http://www.drugbank.ca/drugs/DB00574
http://www.drugbank.ca/drugs/DB00574#targets
http://www.drugbank.ca/drugs/DB00574#enzymes

3. ## NCI Thesaurus (NCIt)

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> https://www.cancer.gov/policies/copyright-reuse

Fenfluramine
https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C81418

4. ## ChemIDplus

Fenfluramine [INN:BAN]
https://chem.nlm.nih.gov/chemidplus/sid/0000458242

ChemIDplus Chemical Information Classification
https://chem.sis.nlm.nih.gov/chemidplus/

5. ## EPA DSSTox

> LICENSE
> https://www.epa.gov/privacy/privacy-act-laws-policies-and-resources

Fenfluramine
https://comptox.epa.gov/dashboard/DTXSID4023044

6. ## European Chemicals Agency (ECHA)

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> https://echa.europa.eu/web/guest/legal-notice

fenfluramine hydrochloride
https://echa.europa.eu/substance-information/-/substanceinfo/100.006.336

fenfluramine
https://echa.europa.eu/substance-information/-/substanceinfo/100.006.616

Fenfluramine hydrochloride

https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/31889

Fenfluramine
https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/89474

7. ## HSDB

FENFLURAMINE
https://pubchem.ncbi.nlm.nih.gov/source/hsdb/3080

8. ## ClinicalTrials.gov

https://clinicaltrials.gov/

9. ## Drug Gene Interaction database (DGIdb)

http://www.dgidb.org/drugs/FENFLURAMINE

10. ## EU Community Register of Medicinal Products

Fenfluramine
https://ec.europa.eu/health/documents/community-register/html/ho1044.htm

11. ## EPA Chemical and Products Database (CPDat)

fenfluramine
https://comptox.epa.gov/dashboard/DTXSID4023044#exposure

EPA CPDat Classification
https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

12. ## EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/

13. ## MassBank of North America (MoNA)

Fenfluramine
http://mona.fiehnlab.ucdavis.edu/spectra/browse?inchikey=DBGIVFWFUFKIQN-UHFFFAOYSA-N

14. ## SpectraBase

https://spectrabase.com/spectrum/JSSLtqE6ZDK
https://spectrabase.com/spectrum/5ahAEAnbpns
https://spectrabase.com/spectrum/D7jVddYbbKL
https://spectrabase.com/spectrum/2HjydamfyGq

15. ## NIST Mass Spectrometry Data Center

Fenfluramine
http://www.nist.gov/srd/nist1a.cfm

16. ## Springer Nature

17. ## Thieme Chemistry

18. WHO ATC

https://www.whocc.no/atc/

ATC Code
https://www.whocc.no/atc_ddd_index/

19. Wikipedia

fenfluramine
https://en.wikipedia.org/wiki/Fenfluramine

20. MeSH

Fenfluramine
https://www.ncbi.nlm.nih.gov/mesh/68005277

MeSH Tree
http://www.nlm.nih.gov/mesh/meshhome.html

Serotonin Uptake Inhibitors
https://www.ncbi.nlm.nih.gov/mesh/68017367

Serotonin Agents
https://www.ncbi.nlm.nih.gov/mesh/68018490

21. PubChem

https://pubchem.ncbi.nlm.nih.gov

22. KEGG

Anatomical Therapeutic Chemical (ATC) classification
http://www.genome.jp/kegg-bin/get_htext?br08303.keg

Target-based classification of drugs
http://www.genome.jp/kegg-bin/get_htext?br08310.keg

Drug Classes
http://www.genome.jp/kegg-bin/get_htext?br08330.keg

23. WIPO

International Patent Classification
http://www.wipo.int/classifications/ipc/

24. UN Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

GHS Classification Tree
http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

25. IUPHAR/BPS Guide to PHARMACOLOGY

Target Classification
http://www.guidetopharmacology.org/

26. PATENTSCOPE (WIPO)

SID 403413004
https://pubchem.ncbi.nlm.nih.gov/substance/403413004

27. NCBI

https://www.ncbi.nlm.nih.gov/projects/linkout