



Critical review report:
2-Fluorodeschloroketamine

Expert Committee on Drug Dependence
Forty-sixth Meeting
Geneva, 16–20 October 2023

This report represents the views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

© World Health Organization 2023
All rights reserved.

This advance copy was distributed to the members of the 46th Expert Committee on Drug Dependence before its formal publication by the World Health Organization. The document may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means without the permission of the World Health Organization.

The designations used and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

DRAFT

Contents

Executive summary	4
1 Substance identification	6
A International nonproprietary name	6
B Chemical Abstracts Service (CAS) registry number	6
C Other chemical names	6
D Trade names	6
E Street names	6
F Physical appearance	6
G WHO review history	6
2 Chemistry	6
A Chemical name	6
B Chemical structure	8
C Stereoisomers	8
D Methods and ease of illicit manufacture	8
E Chemical properties	9
F Identification and analysis	9
3 Ease of conversion to controlled substances	10
4 General pharmacology	11
A Routes of administration and dosage	11
B Pharmacokinetics	11
C Pharmacodynamics	11
5 Toxicology	11
6 Adverse reactions in humans	12
7 Dependence potential	12
A Studies in experimental animals	12
B Studies in humans	12
8 Abuse potential	12
A Studies in experimental animals	12
B Studies in humans	13
9 Therapeutic applications, extent of therapeutic use and epidemiology of medical use	13
10 Listing on the WHO Model List of Essential Medicines	13
11 Marketing authorizations (as a medicinal product)	14
12 Industrial use	14
13 Non-medical use, abuse and dependence	14
14 Nature and magnitude of public health problems related to misuse, abuse and dependence	14
15 Licit production, consumption and international trade	14
16 Illicit manufacture and traffic and related information	14
17 Current international controls and their impact	15
18 Current and past national controls	15
19 Other medical and scientific matters relevant for a recommendation on scheduling of the substance	15
References	15

Executive summary

2-Fluorodeschloroketamine (IUPAC name: 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one) is an arylcyclohexylamine that is chemically related to the dissociative anaesthetic ketamine. 2-Fluorodeschloroketamine contains a chiral centre; thus, two enantiomers may exist: (*R*)- and (*S*)-2-fluorodeschloroketamine. No information is available on the enantiomeric composition of 2-fluorodeschloroketamine circulating on the drug market, but it is probably available as a racemic mixture of the (*R*)- and (*S*)-enantiomers. 2-Fluorodeschloroketamine was synthesized in 2014, and the first documented detection by government authorities was in Spain in 2016. Since then, the compound has been detected in products or in biological samples in at least 11 countries: Australia, Austria, Canada, China, Denmark, Finland, France, Italy, Netherlands (Kingdom of the), the United Kingdom (Wales) and the USA. While 2-fluorodeschloroketamine is not under international control, it is regulated under national psychoactive drug control regulations in Austria, Canada, China, Germany, Italy, Latvia, Switzerland, Turkey and the United Kingdom.

The available data, including reports from people who use 2-fluorodeschloroketamine and law enforcement seizures, indicates that it is usually purchased in the form of crystals or powder. Crystals may be crushed and the powder may be placed in capsules; either may be solubilized. Common routes of administration include insufflation (direct snorting of powder or crushed crystals or solubilization into a nasal spray) and oral, less commonly mentioned routes being intramuscular, sublingual and rectal insertion. Information websites for users list a dosage range according to intoxicating effects: “light” (20–50 mg), “common” (50–100 mg) and “strong” (100–175 mg). The onset of effects after insufflation is estimated to be 20–40 min, and the duration of action is 1–3 h. The basis for this information is not clear, and, given its anecdotal nature, caution is suggested in interpreting it.

After administration, 2-fluorodeschloroketamine undergoes extensive hepatic biotransformation, with *N*-dealkylation, oxidation and reduction as the primary phase-I reactions and *N*-glucuronidation of the *N*-dealkylated metabolites as the primary phase-II reactions. Its primary metabolites include nor-2-fluorodeschloroketamine, dihydro-2-fluorodeschloroketamine, dihydro-nor-2-fluorodeschloroketamine and dehydroamine-nor-2-fluorodeschloroketamine. While the time course of 2-fluorodeschloroketamine in humans has not been assessed, its estimated in-vitro half-life after exposure to human liver microsomes was 69.1 min, with an intrinsic clearance rate of 9.2 ml/min per kg. 2-Fluorodeschloroketamine showed less protein binding and predicted lipophilicity than ketamine.

Studies of the pharmacodynamics of 2-fluorodeschloroketamine have focused on evaluation of its abuse potential. Although it is widely assumed that 2-fluorodeschloroketamine is a noncompetitive antagonist at *N*-methyl-D-aspartate receptors, no confirmatory in-vitro binding or functional data are available. In-vivo research consists of two published studies of the effects of the compound in preclinical procedures designed to evaluate the abuse potential of psychoactive drugs. 2-Fluorodeschloroketamine induced conditioned place preference in mice and ketamine-like discriminative stimulus effects and locomotor sensitization in rats. Further, it was self-administered (intravenously) by rats, with an inverted U-shaped dose–effect curve that is characteristic of some classes of abused drugs. After a period of extinction, self-administration was reinstated by exposure to cues previously associated with delivery of the drug and by systemic injection of a psychoactive dose before a self-administration session. Its potency in all procedures was similar to that of ketamine. The toxicology of 2-fluorodeschloroketamine has not been studied.

The presence of measurable concentrations of 2-fluorodeschloroketamine in post-mortem blood samples and in biological samples from impaired drivers and clinical admissions has been reported by several sources. In some cases, other drugs were also detected (including ketamine and other ketamine analogues); however, 2-fluorodeschloroketamine was the only substance detected in at least one fatality in Finland and the probability of causality was considered high. Several published case reports have reported central nervous system (CNS) or behavioural effects, included dissociation, confusion, agitation,

combativeness, nystagmus, hallucinations and impaired or loss of consciousness; the cardiovascular effects were tachycardia and hypertension; other effects included nausea and vomiting. The extent to which 2-fluorodeschloroketamine directly contributed to these observed or reported effects is uncertain, as laboratory analysis confirmed the presence of other substances in biological samples from most patients. The predominant effects of 2-fluorodeschloroketamine described by people who used it include dissociation, tranquility, happiness and numbness and tingling in the periphery. Lost sense of time, loss of motor control and colourful visual or vivid auditory hallucinations have also been mentioned. Similarities to the subjective effects of ketamine were noted by several people who had used both drugs. Posts on online forums self-reporting experience of use of 2-fluorodeschloroketamine should be considered anecdotal, as there was no analytical confirmation of sole use.

The first appearance of 2-fluorodeschloroketamine in Europe was noted in 2016, while the substance was analytically verified in biological samples collected in the USA in 2019. In China, where ketamine has been a prominent drug of abuse since the early 2000s, at least 60 cases of analytically confirmed exposure to 2-fluorodeschloroketamine have been reported in recent years. In 19 of 20 cases reported in one study, co-use with ketamine or another ketamine analogue was reported after analysis of biological samples. A trend towards increasing use by young females in China was noted, although use by males predominated. Analysis of wastewater in several cities in southern China confirmed continuous use of 2-fluorodeschloroketamine during a 2-year sampling period in 2018–2020.

1 Substance identification

A *International nonproprietary name*

Not assigned

B *Chemical Abstracts Service (CAS) registry number*

111982-50-4 (free base)
2657761-05-0 ((2S)-enantiomer)
2657761-04-9 ((2R)-enantiomer)
111982-49-1 (hydrochloride salt)

C *Other chemical names*

2-(2-Fluorophenyl)-2-(methylamino)cyclohexanone (ACI)
2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one
Cyclohexanone, 2-(2-fluorophenyl)-2-(methylamino)-
2-Fluorodeschloroketamine
2-Fluoroketamine
Fluoroketamine
2-FDCK
2F-DCK
2-FL-2'-OXO-PCM

D *Trade names*

2-Fluorodeschloroketamine is sold under its own chemical names.

E *Street names*

2-Fluorodeschloroketamine is available on the Internet, sold under various names, including “2-fluoroketamine”, “2FDCK” and “2-FK”, or as “ketamine” (1).

F *Physical appearance*

The free base pure has been described as a brown oil (2). The hydrochloride salt is described as a crystalline solid (3) or a white powder (4).

2-Fluorodeschloroketamine for recreational use is distributed mainly as crystals or powder. Recently, chocolates containing 2-fluorodeschloroketamine and other new psychoactive substances (NPS) were seized in China (5).

G *WHO review history*

2-Fluorodeschloroketamine has not been formally reviewed by WHO and is not currently under international control.

2 Chemistry

A *Chemical name*

IUPAC name:

2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one

Chemical Abstracts index name:

Cyclohexanone, 2-(2-fluorophenyl)-2-(methylamino)- (9CI, ACI)

Free base

Canonical SMILES

O=C1CCCCC1(NC)C=C=CC=C2F

InChI

InChI=1S/C13H16FNO/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14/h2-3,6-7,15H,4-5,8-9H2,1H3

InChI key

PHFAGYYTDLITTB-UHFFFAOYSA-N

Hydrochloride salt

Canonical SMILES

Cl.O=C1CCCCC1(NC)C=C=CC=C2F

InChI

InChI=1S/C13H16FNO.ClH/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14;/h2-3,6-7,15H,4-5,8-9H2,1H3;1H

InChI key

FQOFLBNEXJTBJE-UHFFFAOYSA-N

(2R)-enantiomer

Canonical SMILES

O=C1CCCCC1(NC)C=C=CC=C2F

Isomeric SMILES

N(C)[C@]1(C(=O)CCCC1)C2=C(F)C=CC=C2

InChI

InChI=1S/C13H16FNO/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14/h2-3,6-7,15H,4-5,8-9H2,1H3/t13-/m1/s1

InChI key

PHFAGYYTDLITTB-CYBMUJFWSA-N

(2S)-enantiomer

Canonical SMILES

O=C1CCCCC1(NC)C=C=CC=C2F

Isomeric SMILES

N(C)[C@]1(C(=O)CCCC1)C2=C(F)C=CC=C2

InChI

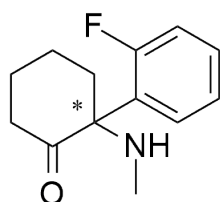
InChI=1S/C13H16FNO/c1-15-13(9-5-4-8-12(13)16)10-6-2-3-7-11(10)14/h2-3,6-7,15H,4-5,8-9H2,1H3/t13-/m0/s1

InChI Key

PHFAGYYTDLITTB-ZDUSSCGKSA-N

B Chemical structure

Free base:

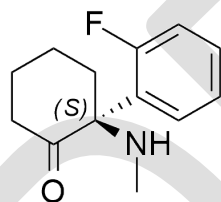


Molecular formula: $C_{13}H_{16}FNO$

Molecular weight: 221.27 g/mol

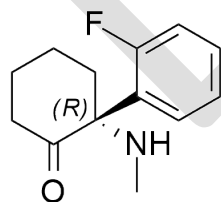
C Stereoisomers

2-Fluorodeschloroketamine contains a chiral centre; therefore, two enantiomers may exist: (*R*)-2-Fluorodeschloroketamine and (*S*)-2-Fluorodeschloroketamine. No information is available on the enantiomeric composition of 2-fluorodeschloroketamine circulating on the drug market but it is probably available as a racemic mixture of the (*R*)- and (*S*)- enantiomers. Individual stereoisomers cannot be excluded.



2657761-05-0

(2*S*)-2-(2-Fluorophenyl)-2-(methylamino)cyclohexan-1-one



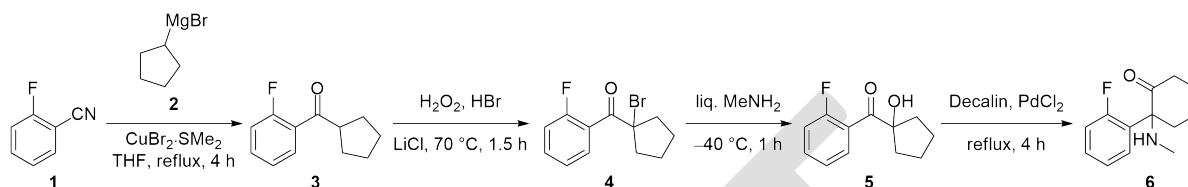
2657761-04-9

(2*R*)-2-(2-Fluorophenyl)-2-(methylamino)cyclohexan-1-one

D Methods and ease of illicit manufacture

2-Fluorodeschloroketamine is an analogue of ketamine in which the chlorine atom is replaced by a fluorine atom. The first synthesis was reported in 1987 by Dimitrov et al. (6), who prepared the material in several steps, starting from 2-fluorobenzoyl chloride; however, no details were given.

Later, 2-fluorodeschloroketamine was synthesized by Moghimi et al. (2), who reported the reaction conditions shown in scheme 1. Synthesis started with reaction of 2-fluorobenzonitrile (1) and the Grignard reagent cyclopentylmagnesium bromide (2) to give 2-fluorophenyl-cyclopentyl ketone (3), which was brominated in the α position. The resulting α -bromo ketone 4 reacted with methylamine to form the α -hydroxy imine (5). Thermal rearrangement of the imine hydroxide to 2-fluorodeschloroketamine (6) was obtained by heating at high temperature in decalin with the addition of PdCl_2 as a catalyst.



Scheme 1. Synthesis of 2-fluorodeschloroketamine

No information was available on the routes of synthesis used for the 2-fluorodeschloroketamine products circulating on the market, although (2''-fluorophenyl)(methylimino) methyl]cyclopentan-1-ol was reported to have been seized at a production site as a suspected chemical precursor of 2-fluorodeschloroketamine (7). This suggests that the synthetic route used is that shown in scheme 1. The procedure leads to the formation of the racemic mixture of 2-fluorodeschloroketamine.

Although the synthesis is simple and does not require controlled precursors, it must be carried out in a synthetic chemistry laboratory by qualified personnel.

E Chemical properties

Melting-point

Hydrochloride salt

258–260 °C (2)

Boiling-point

No information was found.

Solubility

Hydrochloride salt

Soluble in dimethylformamide (10 mg/mL), dimethylsulfoxide (5 mg/mL), ethanol (5 mg/mL), methanol (1 mg/mL), and phosphate-buffered saline (pH 7.2, 10 mg/mL) (3).

Partially soluble in dichloromethane and soluble in methanol and water (10).

F Identification and analysis

Reference material and pure compound

2-Fluorodeschloroketamine hydrochloride salt and its urinary metabolite 2-fluorodeschloronorketamine hydrochloride are available as reference materials from commercial suppliers for use in routine methods of analysis for forensic and clinical investigations (3,9).

2-Fluorodeschloroketamine hydrochloride as a pure compound was fully characterized by gas chromatography coupled to mass spectrometry (GC-MS) (electron ionization), liquid chromatography (LC) coupled to high-resolution mass spectrometry (quadrupole time-of-flight [QToF]), Fourier-transform infrared and nuclear magnetic resonance (^1H and ^{13}C NMR) spectroscopy (2,10).

Separation of the two enantiomers of 2-fluorodeschloroketamine has been reported by LC-ultraviolet in a chiral stationary phase (11).

Seized material

Seized material has been analysed for 2-fluorodeschloroketamine with several techniques, including direct analysis in real-time MS (DART-MS) and GC-MS, specifically on two powders (white crystals) purchased on the Internet and sold as bucinnazine. One sample was identified as 2-fluorodeschloroketamine (12). Gao et al. (13) analysed 78 seized samples in China by LC-high-resolution MS (HRMS) and confirmed the identification by NMR.

GC-MS and quantitative NMR were used for determination of 2-fluorodeschloroketamine in seized chocolate samples (5).

Trace residues of 2-fluorodeschloroketamine were found in an analysis by DART-MS and MS/MS of over 1000 discarded drug packaging samples taken at large public events (14).

2-Fluorodeschloroketamine has been identified and quantified in wastewater by GC-MS and was found to be stable in wastewater for 15 days at room temperature and pH 7 and pH 2 (15). Li et al. (16) reported quantification of 2-fluorodeschloroketamine and its urinary metabolite 2-fluorodeschloronorketamine by LC coupled with triple quadrupole MS (LC-QqQ) in wastewater.

Biological samples

Several analytical methods based on the LC-HRMS technique, particularly QToF and Orbitrap, have been reported for the identification and quantification of 2-fluorodeschloroketamine in biological samples, including blood from people driving under the influence of drugs and forensic hair samples (17), one patient's urine (1) and post-mortem blood and hair samples from a forensic case of suicide (18). The authors of the last study presumptively identified the nor-, dihydro- and nor-dihydro metabolites and reported that the parent compound in blood and hair was stable in an autosampler for at least 48 h (18). Hair samples from a cohort of pregnant women in Mexico were tested for various NPS by LC-HRMS and found to contain 2-fluorodeschloroketamine (19). LC-QToF was used for forensic toxicology testing of over 3000 biological samples, including blood, urine, serum/plasma and tissue matrices (20).

LC coupled to low-resolution MS, particularly tandem MS with-QqQ was used to quantify 2-fluorodeschloroketamine in nail samples from nearly 300 people who used drugs in China (21). LC-MS-MS in dynamic multiple reaction monitoring mode was fully validated for simultaneous detection of 163 substances in blood (120 NPS and 43 other drugs) (22). In this work, 2-fluorodeschloroketamine was reported to be stable in blood for 1 month at $-25\text{ }^\circ\text{C}$. An LC-MS/MS method was validated for the analysis of 11 drugs of abuse, 2-fluorodeschloroketamine, in urine (23).

3 Ease of conversion to controlled substances

No information was found on whether 2-fluorodeschloroketamine can be converted into a controlled substance.

4 General pharmacology

A Routes of administration and dosage

The available data, including reports from people who used 2-fluorodeschloroketamines and law enforcement seizures, 2-fluorodeschloroketamine is usually purchased in the form of crystals or powder. The crystals may be crushed or the powder may be placed in capsules, and both may be solubilized. Common routes of administration include insufflation (direct snorting of powder or crushed crystals or solubilization into a nasal spray) and oral; less commonly mentioned routes are intramuscular injection, sublingual and rectal insertion (24–26).

No studies were found on human dosages; however, one informational website has categorized doses according to their intoxicating effects after insufflation as “light” (20–50 mg), “common” (50–100 mg) and “strong” (100–≥ 175 mg) (27). The website also listed the following doses of ketamine: “light” (20–50 mg), “common” (50–125 mg) and “strong” (125–175 mg) (28). The onset of effects is estimated to occur 20–40 min after insufflation; the duration of action is 1–3 h; and the after-effects last for 1–3 h (27). The basis for this information is not clear, and, given its anecdotal nature, caution is suggested in interpreting these data.

B Pharmacokinetics

No information was available on the absorption and distribution of 2-fluorodeschloroketamine. Several studies have been conducted of its metabolism in vitro (human liver microsomes or human hepatocytes) and in vivo (analysis of biological samples). The results show that 2-fluorodeschloroketamine undergoes extensive hepatic biotransformation in the body. The number of identified phase-I and -II metabolites ranged from 3 to 26, depending on the assay. *N*-Dealkylation, oxidation and reduction are the primary phase-I reactions, and *N*-glucuronidation of the *N*-dealkylated metabolites are the primary phase-II reactions (29). The main metabolites in several studies and assays were nor-2-fluorodeschloroketamine, dihydro-2-fluorodeschloroketamine, dihydro-nor-2-fluorodeschloroketamine and dehydroamine-nor-2-fluorodeschloroketamine (18,30–33). It is not known whether these metabolites are psychoactive.

While the time course of 2-fluorodeschloroketamine has not been assessed in humans, its estimated in-vitro half-life after exposure to human liver microsomes was 69.1 ± 13.1 min, with an intrinsic clearance rate of 9.2 ± 1.7 mL/min per kg (17). 2-Fluorodeschloroketamine showed less protein binding than ketamine, with measured unbound fractions (f_u) of 0.54 and 0.79 for the two compounds, respectively (17). Similarly, the predicted lipophilicity of 2-fluorodeschloroketamine was less than that of ketamine (predicted logP = 2.89 and 3.35, respectively). Protein binding and lipophilicity would be expected to affect the absorption and distribution of these substances as well as their time courses.

C Pharmacodynamics

Little information is available on the pharmacodynamics of 2-fluorodeschloroketamine. No in-vitro binding or functional data are available. Two published studies examined the effects of the compound in several preclinical procedures designed to evaluate the abuse potential of psychoactive drugs. The results are described in section 8A of this report.

5 Toxicology

No studies of the preclinical toxicology of 2-fluorodeschloroketamine were available.

6 Adverse reactions in humans

Measurable concentrations of 2-fluorodeschloroketamine have been reported in post-mortem blood samples and in biological samples from impaired drivers and clinical admissions by several sources (17,30–38). In some cases, other drugs were also detected (including ketamine and other ketamine analogues). 2-Fluorodeschloroketamine was the only substance detected in at least one fatality in Finland (39), and the likelihood of causality was high according to the system used to rate the contribution of a substance to the outcome; further details were lacking. Several case reports provide additional information on the disposition of patients observed by medical or law enforcement personnel while under the influence of 2-fluorodeschloroketamine. The symptoms tend to cluster into three categories: CNS, cardiovascular and other. The reported CNS and behavioural effects included dissociation, confusion, agitation, combativeness, nystagmus, hallucinations and impaired or loss of consciousness; the reported cardiovascular effects were tachycardia and hypertension; other effects included nausea and vomiting (30,33,34). The extent to which 2-fluorodeschloroketamine contributed directly to these observed or reported effects is uncertain, as the presence of other substances in the biological samples of most of the patients was confirmed by laboratory analysis.

The predominant effects of 2-fluorodeschloroketamine described by people who have used it include dissociation, tranquility, happiness and numbness and tingling in the periphery (24–26). Lost sense of time, loss of motor control and colourful visual or vivid auditory hallucinations have also been mentioned. Similarities to the subjective effects of ketamine were noted by several people who had used both drugs. Other subjective experiences reported by users include confusion, agitation and memory loss (40). Posts on online forums of self-reported experience of use of 2-fluorodeschloroketamine should be considered as anecdotal, as no analytical confirmation of sole use was obtained.

7 Dependence potential

A Studies in experimental animals

No information was found.

B Studies in humans

No information was found.

8 Abuse potential

A Studies in experimental animals

2-Fluorodeschloroketamine has been examined in several preclinical procedures designed to evaluate the abuse potential of psychoactive drugs. In each model, its potency was roughly equivalent to that of ketamine.

In a conditioned place preference procedure, which is sometimes used to assess the rewarding effects of a drug according to the principles of classical conditioning, 2-fluorodeschloroketamine dose-dependently induced conditioned place preference (as compared with vehicle) in male ICR mice in a three-compartment procedure (41). The minimum effective dose of both 2-

fluorodeschloroketamine and ketamine was 3 mg/kg (intraperitoneally [i.p.]). At this dose, neither drug affected locomotor activity in mice.

Locomotor sensitization is a phenomenon whereby, rodents show enhanced sensitivity to the locomotor stimulant effects of a drug after repeated dosing and a period of drug withdrawal. When tested acutely in male Sprague-Dawley rats, a 30 mg/kg (i.p.) dose of 2-fluorodeschloroketamine significantly increased locomotor activity. During repeated dosing with 2-fluorodeschloroketamine (1–30 mg/kg, i.p.), locomotor activity remained constant; however, during a challenge test conducted after 2 weeks of abstinence, 30 mg/kg (i.p.) 2-fluorodeschloroketamine increased locomotion (41). Ketamine had similar effects at the same doses. These findings suggest induction of locomotor sensitization, a pharmacological effect that is characteristic of psychomotor stimulants.

Drug discrimination is a pharmacologically selective animal model of the subjective effects of psychoactive drugs in humans. In a study using male Sprague-Dawley rats trained to discriminate ketamine (5 mg/kg, i.p.) from vehicle in a standard two-nose-poke procedure, 2-fluorodeschloroketamine produced full dose-dependent substitution for the ketamine training dose, with an ED₅₀ of 1.605 mg/kg (i.p.) and a maximum percentage of responding on the ketamine-associated aperture of 97.25% at a 2.5 mg/kg dose (41). The ED₅₀ of ketamine in this procedure was 2.185 mg/kg. These results suggest that 2-fluorodeschloroketamine has subjective effects in humans similar to those of ketamine.

In the same study, 2-fluorodeschloroketamine and ketamine were assessed in separate groups of male Sprague-Dawley rats trained to self-administer the respective training drug at an intravenous dose of 0.5 mg/kg per infusion (41). Rats self-administered both drugs, with an inverted U-shaped dose–effect function. The peak number of infusions of both drugs occurred at 1 mg/kg/infusion. In a study using a behavioural economics strategy, 2-fluorodeschloroketamine and ketamine showed similar reinforcing efficacy in male Sprague-Dawley rats trained to self-administer the drugs (0.5 mg/kg/infusion) (42). In further tests, 2-fluorodeschloroketamine resulted in reinstatement after extinction induced by previous cues paired with drug delivery and when primed by a pre-session i.p. injection of the drug. Western blot analysis of the nucleus accumbens of the rats showed downregulation of CREB/BDNF and upregulation of phosphorylation of the Akt/mTOR/GSK-3 β signalling pathway, suggesting mechanisms for the observed reinstatement.

B Studies in humans

No information was found.

9 Therapeutic applications, extent of therapeutic use and epidemiology of medical use

2-Fluorodeschloroketamine has no known therapeutic uses.

10 Listing on the WHO Model List of Essential Medicines

2-Fluorodeschloroketamine is not listed on the 22nd WHO Model List of Essential Medicines or on the 8th WHO Model List of Essential Medicines for Children.

11 Marketing authorizations (as a medicinal product)

2-Fluorodeschloroketamine has no known marketing authorization.

12 Industrial use

2-Fluorodeschloroketamine has no known industrial use.

13 Non-medical use, abuse and dependence

2-Fluorodeschloroketamine is a ketamine analogue that was synthesized in 2014 (2) and appeared on the European illicit drug market in Spain in 2016 (43). Reports on online forums by people who use drugs provide evidence that 2-fluorodeschloroketamine has been used intentionally for its intoxicating effects (see section 6). This substance has been detected in seized and biological samples in at least 11 countries (see section 16 for list). The prevalence of chronic use of and dependence on 2-fluorodeschloroketamine has not been reported.

14 Nature and magnitude of public health problems related to misuse, abuse and dependence

Since its emergence as a novel psychoactive substance in 2016, 2-fluorodeschloroketamine has been confirmed analytically in post-mortem samples as well as in samples collected from impaired drivers and emergency department admissions in several countries, including Australia (39), Canada (39), China (33,38), Denmark (17), Finland (39), France (39), Italy (18,44) and the USA (34,39).

Between July 2019 and May 2022, 11 cases (five post-mortem) including analytically confirmed 2-fluorodeschloroketamine were reported to the Early Warning System Tox-Portal (39). 2-Fluorodeschloroketamine was the only listed substance detected in four cases. In three of the nonfatal cases and two of the fatalities, 2-fluorodeschloroketamine was designated as contributory (medium) on the causality scale used in the system. In two fatalities (in Finland and in France), the effects of 2-fluorodeschloroketamine were determined to be causal (high), and this drug was the only substance listed in the case in Finland. Between January and April 2020, 2-fluorodeschloroketamine was the sole (or one of only a few) substance(s) detected in six samples analysed by Welsh authorities (40) and in 35 samples analysed in a laboratory based in the USA (45).

15 Licit production, consumption and international trade

No information was found.

16 Illicit manufacture and traffic and related information

In China, where ketamine has been a prominent drug of abuse since the early 2000s, at least 60 cases of analytically confirmed exposure to 2-fluorodeschloroketamine have been reported recently (33,37,38). In 19 of 20 cases involving 2-fluorodeschloroketamine reported in one study, use with ketamine or another ketamine analogue was found by analysis of biological samples (33). A trend of increasing use by young females in China was noted, although use by males predominated (38).

Analysis of wastewater in several cities in southern China confirmed continuous use of 2-fluorodeschloroketamine over a 2-year sampling period (2018–2020) (15).

In Europe, 2-fluorodeschloroketamine was first reported in 2016 (29), and its presence was analytically verified in biological samples collected in the USA in 2019 (34). Samples containing 2-fluorodeschloroketamine submitted to an anonymous testing site (between 2017 and the present) were received from Austria (n=7), Canada (n=1), China (n=8), Netherlands (Kingdom of the, n=1), the United Kingdom (n=1) and the USA (n=5) (45). As submission of samples was voluntary, the distribution of sites of origin may not represent the global distribution or trafficking of 2-fluorodeschloroketamine. Other countries in which 2-fluorodeschloroketamine has been detected as a product sample or measured in biological samples include Australia (39), Denmark (17), Finland (39), France (39) and Italy (18,44).

17 Current international controls and their impact

2-Fluorodeschloroketamine is not currently under international control.

18 Current and past national controls

2-Fluorodeschloroketamine is regulated under national psychoactive drug control regulations in Austria, Canada, China, Germany, Italy, Latvia, Switzerland, Turkey, and the United Kingdom (32,46). 2-Fluorodeschloroketamine does not appear to be controlled under national regulations in other countries.

19 Other medical and scientific matters relevant for a recommendation on scheduling of the substance

One of 65 chocolate samples submitted to the National Anti-Drug Laboratory of China for analysis was found to contain 2-fluorodeschloroketamine (5). No information was provided on the source of the chocolate samples or on the prevalence. The presence of 2-fluorodeschloroketamine and other novel psychoactive substances in food may increase the risk of unintentional exposure (including paediatric).

References

1. Tang MHY, Li TC, Lai CK, Chong YK, Ching CK, Mak TWL. Emergence of new psychoactive substance 2-fluorodeschloroketamine: Toxicology and urinary analysis in a cluster of patients exposed to ketamine and multiple analogues. *Forensic Sci Int.* 2020;12:110327.
2. Moghimi A, Rahmani S, Zare R, Sadeghzadeh M. Synthesis of 2-(2-fluorophenyl)-2-methylamino-cyclohexanone as a new ketamine derivative. *Synthet Communications.* 2014;44:2021–8.
3. 2-Fluoro deschloroketamine (hydrochloride) (Item No. 19786) [Online]. Ann Arbor (MI): Cayman Chemicals; 2017 ([https://www.caymanchem.com/product/19786/2-fluoro-deschloroketamine-\(hydrochloride\)](https://www.caymanchem.com/product/19786/2-fluoro-deschloroketamine-(hydrochloride)), accessed 10 July 2023).
4. Analytical report: 2-fluoro deschloroketamine (C₁₃H₁₆FNO) (2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one). Ljubljana: Slovenian National Forensic Laboratory; 2017 (https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/2-fluoro%20Deschloroketamine-ID-1847-17_report.pdf).

5. Song CH, Jia W, Liu CM, Hua ZD, Meng X, Zhao YB et al. New trends of new psychoactive substances (NPS)-infused chocolate: Identification and quantification of trace level of NPS in complex matrix by GC-MS and NMR. *Talanta*. 2023;255:124257.
6. Dimitrov I, Denny WA, Jose J. Syntheses of ketamine and related analogues: a mini review. *Synthesis*. 2018;50:4201–15.
7. Luo X, Zhang D, Luo Q, Huang K, Liu X, Yang N et al. Structure identification and analysis of the suspected chemical precursor of 2-fluorodeschloroketamine and its decomposition products. *Drug Test Anal*. 2022;14:1065–78.
9. 2-Fluoro deschloronorketamine (hydrochloride) (Item No. 29118) [Online]. Ann Arbor (MI): Cayman Chemicals; 2019 ([https://www.caymanchem.com/product/29118/2-fluoro-deschloronorketamine-\(hydrochloride\)](https://www.caymanchem.com/product/29118/2-fluoro-deschloronorketamine-(hydrochloride)), accessed 10 July 2023).
10. Analytical report: 2F-ketamine (C₁₃H₁₆FNO) 2-(2-fluorophenyl)-2-(methylamino)cyclohexan-1-one. Ljubljana: Slovenian National Forensic Laboratory; 2017 (https://www.policija.si/apps/nfl_response_web/0_Analytical_Reports_final/2-fluoro%20Deschloroketamine-ID-1847-17_report.pdf).
11. Hägele JS, Basrak M, Schmid MG Enantioselective separation of novel psychoactive substances using a Lux® AMP 3 µm column and HPLC-UV. *J Pharmaceut Biomed Anal*. 2020;179:112967.
12. Resnik KN, Babb KN, Bekenstein LW, Moeller FG, Peace MR, Alves EA. Case report: Identification of AP-238 and 2-fluorodeschloroketamine in internet available powder samples sold as bucinnazine. *Forensic Sci Int*. 2023;348:111732.
13. Gao J, Xu B, Yang R, Zhang H Screening strategy for ketamine-based new psychoactive substances using fragmentation characteristics from high resolution mass spectrometry. *Forensic Sci Int*. 2023;347:111677.
14. West H, Fitzgerald J, Hopkins K, Li E, Clark N, Tzanetis S et al. Early warning system for illicit drug use at large public events: trace residue analysis of discarded drug packaging samples. *J Am Soc Mass Spectrom*. 2021;32:2604–14.
15. Shao XT, Yu H, Lin JG, Kong XP, Wang Z, Wang DG. Presence of the ketamine analog of 2-fluorodeschloroketamine residues in wastewater. *Drug Test Anal*. 2021;13:1650–7.
16. Li X, Feng L, Fan X, Huang J, Du Y. Wastewater-based monitoring of 2-fluoro-deschloroketamine abuse from 2019 to 2021 in a southern Chinese province. *Sci Total Environ*. 2022;826:154191.
17. Davidsen AB, Mardal M, Holm NB, Andreasen AK, Johansen SS, Noble C et al. Ketamine analogues: comparative toxicokinetic in vitro-in vivo extrapolation and quantification of 2-fluorodeschloroketamine in forensic blood and hair samples. *J Pharm Biomed Anal*. 2020;180:113049.
18. Mestria S, Odoardi S, Biosa G, Valentini V, Di Masi G, Cittadini F et al. Method development for the identification of methoxpropamine, 2-fluoro-deschloroketamine and deschloroketamine and their main metabolites in blood and hair and forensic application. *Forensic Sci Int*. 2021;323:110817.
19. Marchei E, Rotolo MC, Mannocchi G, Capomassi A, Gómez-Ruiz LM, Acosta-López A et al. Assessment of licit and illicit drugs consumption during pregnancy by ultra-high performance liquid chromatography–high resolution mass spectrometry (UHPLC-HRMS) target screening in Mexican women hair. *J Pharm Biomed Anal*. 2022;211:114607.
20. Krotulski AJ, Varnum SJ, Logan BK. Sample mining and data mining: combined real-time and retrospective approaches for the identification of emerging novel psychoactive substances. *J Forens Sci*. 2020;65:550–62.
21. Liu P, Liu W, Qiao H, Jiang S, Wang Y, Chen J et al. Simultaneous quantification of 106 drugs or their metabolites in nail samples by UPLC-MS/MS with high-throughput sample preparation: Application to 294 real cases. *Anal Chim Acta*. 2022;1226:340170.
22. Vaiano F, Bertol E, Mineo M, Pietrosevoli L, Rubicondo J, Supuran CT et al. Development of a new LC-MS/MS screening method for detection of 120 NPS and 43 drugs in blood. *Separations*. 2021;8:221.

23. Wong GF, Lee WM, Li CK. Qualitative screening of amphetamine- and ketamine-type abuse drugs in urine employing dual mode extraction column by liquid chromatography–tandem mass spectrometry (LC-MS-MS). *J Anal Toxicol.* 2023;46:1045–52.
24. The Big and Dandy 2-fluorodeschloroketamine (2fk/2fdck) thread. Bluelight; 2023 (<https://bluelight.org/xf/threads/the-big-dandy-2-fluorodeschloroketamine-2fk-2fdck-thread.776753/>, accessed 29 July 2023).
25. 2-Fluorodeschloroketamine reports. Grass Valley (CA): Erowid Center (https://www.erowid.org/experiences/subs/exp_2Fluorodeschloroketamine.shtml#General, accessed 29 July 2023).
26. 2-Fluorodeschloroketamine. San Francisco (CA): Reddit Inc; 2023 (https://www.reddit.com/r/researchchemicals/search/?q=2-fluorodeschloroketamine&restrict_sr=1, accessed 29 July 2023).
27. 2-FDCK. Springfield (PA): Tripsit; 2023 (<https://drugs.tripsit.me/2-fdck>, accessed 28 July 2023).
28. Ketamine. Springfield (PA): Tripsit; 2023 (<https://drugs.tripsit.me/ketamine>, accessed 28 July 2023).
29. Joseph D, Lesueur C, Zerizer F, Fenot A, Alvarez JC, Larabi IA. Characterization of extensive 2-fluorodeschloroketamine (2F-DCK) metabolism in pooled human liver microsomes (pHLM), urine, and hair from an addicted patient using high-resolution accurate mass (HRAM) spectrometry. *J Anal Toxicol.* 2023;47(6):504–16.
30. Domanski K, Fleming SW, Maag H, Bouso Raley E, Debord J, Wright B et al. A psychonaut's experience of intoxication with multiple classes of drugs including novel psychoactive substance 2-fluorodeschloroketamine: case report and urinary analysis. *J Psychoactive Drugs.* 2022 ;54:319–23.
31. Gicquel T, Pelletier R, Richeval C, Gish A, Hakim F, Ferron P et al. Metabolite elucidation of 2-fluorodeschloroketamine (2F-DCK) using molecular networking across three complementary in vitro and in vivo models. *Drug Test Anal.* 2022;14:144–53.
32. Luo X, Zhang D, Zhang F, Luo Q, Huang K, Liu X et al. Comparative analysis and structure identification of oxidative metabolites and hydrogenation metabolite enantiomers for 2-fluorodeschloroketamine. *J Anal Toxicol.* 2023;47:436–47.
33. Tang MHY, Li TC, Lai CK, Chong YK, Ching CK, Mak TWL. Emergence of new psychoactive substance 2-fluorodeschloroketamine: toxicology and urinary analysis in a cluster of patients exposed to ketamine and multiple analogues. *Forensic Sci Int.* 2020;312:110327.
34. Arango E, Toriello A, Rodario Z, Cooper G. Increasing prevalence of ketamine in drivers in New York City including the identification of 2-fluoro-deschloroketamine. *J Anal Toxicol.* 2021;45:799–806.
35. Pelletier R, Le Daré B, Grandin L, Couette A, Ferron P, Morel I et al. New psychoactive substance cocktail in an intensive care intoxication case elucidated by molecular networking. *Clin Toxicol (Phila).* 2022;60:122–5.
36. Pelletier R, Le Daré B, Le Bouëdec D, Kernalléguen A, Ferron PJ, Morel I et al. Arylcyclohexylamine derivatives: pharmacokinetic, pharmacodynamic, clinical and forensic aspects. *Int J Mol Sci.* 2022;23:15574.
37. Li C, Lai CK, Tang MHY, Chan CCK, Chong YK, Mak TWL. Ketamine analogues multiplying in Hong Kong. *Hong Kong Med J.* 2019;25:169.
38. Li Z, Li Z, Xie W, Liu J, Li B, Liu W et al. Hair-based rapid UPLC-MS/MS analysis of 36 phencyclidine-type substances in forensic cases. *J Pharm Biomed Anal.* 2023;234:115577.
39. 2-Fluorodeschloroketamine. Vienna: United Nations Office on Drugs and Crime; 2023 (<https://www.unodc.org/tox/#/admin/search/detailed/%7B%22textQuery%22:%222-fluorodeschloroketamine%22%7D>).
40. 2-Fluorodeschloroketamine. Cardiff: Welsh Emerging Drugs and Identification of Novel Substances Project; 2023 (<https://www.wedinos.org/sample-results#mylocation>, accessed 31 July 2023).
41. Li F, Du H, Wu B, Wei J, Qiao Y, Lai M et al. 2-Fluorodeschloroketamine has similar abuse potential as ketamine. *Addict Biol.* 2022;27:e13171.

42. Du H, Lai M, Zhuang D, Fu D, Zhou Y, Chen S et al. A comparison of reinforcing effectiveness and drug-seeking reinstatement of 2-fluorodeschloroketamine and ketamine in self-administered rats. *Front Mol Neurosci.* 2022;15:972798.
43. EMCDDA–Europol 2016 annual report on the implementation of Council Decision 2005/387/JHA. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2016 (https://www.emcdda.europa.eu/publications/implementation-reports/2016_en, accessed 31 July 2023).
44. Vincenti F, Gregori A, Flammini M, di Rosa F, Salamone A. Seizures of new psychoactive substances on the Italian territory during the COVID-19 pandemic. *Forensic Sci Int.* 2021;326:110904.
45. 2-Fluorodeschloroketamine. Grass Valley (CA): Erowid Center, DrugsData.org; 2023 (https://drugsdata.org/results.php?search_field=all&s=2-fluorodeschloroketamine, accessed 31 July 2023).
46. 2-Fluorodeschloroketamine. Psychonaut Wiki; 2023 (<https://psychonautwiki.org/wiki/2-Fluorodeschloroketamine>, accessed 30 July 2023).

DRAFT