



Critical Review Report:
DOC
(4-Chloro-2,5-dimethoxyamfetamine)

Expert Committee on Drug Dependence
Forty-second Meeting
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Executive Summary

Substance identification

DOC (4-chloro-2,5-dimethoxyamfetamine) (IUPAC name: 1-(4-chloro-2,5-dimethoxyphenyl)propan-2-amine) is the chloro analogue of DOB (4-bromo-2,5-dimethoxyamfetamine) and DOM (2,5-dimethoxy-4-methylamfetamine) which are both listed in Schedule I of the Convention on Psychotropic Substances of 1971. Information obtained from seizures and collections suggests that it has been encountered in powdered and liquid form but that it is predominantly found in the form of LSD-like blotter papers.

WHO Review History

DOC has not been previously pre-reviewed or critically reviewed.

Chemistry

There is no specific information available about the routes of synthesis employed for seized DOC products circulating on the drug market but straightforward methods for its preparation exist without requiring access to precursors that are controlled internationally. The presence of an asymmetric carbon atom gives rise to the (*R*)- and (*S*)-enantiomer and it seems likely for DOC to be most commonly available in the racemic form.

Ease of convertibility into controlled substances

A conversion of DOC into another substance currently listed in any of the international drug conventions might be chemically feasible but specific information is not available.

Similarity to known substances / Effects on the central nervous system

DOC can be considered a classical (serotonergic) hallucinogen and its effects and potency are comparable to the hallucinogenic amfetamines DOB, DOM and DOI (4-iodo-2,5-dimethoxyamfetamine) and to some extent similar to LSD, psilocybin, mescaline and *N,N*-dimethyltryptamine.

General pharmacology

DOC is a potent 5-HT_{2A} receptor agonist with high affinity, a key element in mediating hallucinogenic effects in humans. The available data available so far also indicates that it also binds with high affinity to and activates 5-HT_{2B/2C} receptors. Self-experiments suggested DOC to be active in the 1.5–3.0 mg range with duration of effects estimated to range between 12–24 h. A long duration of effects is also shared by the other hallucinogenic amfetamines DOI, DOB and DOM. DOC is most commonly administered orally and/or sublingually when encountered in the form of blotters. The discriminative stimulus effects of DOC in the drug discrimination paradigm were similar to those of other hallucinogens DOM and *N,N*-dimethyltryptamine but not methamfetamine. Data collected from *in vitro* metabolism studies showed that DOC is transformed into the two *O*-demethylated (2- and 5-position) metabolites. The parent molecule is the preferred analytical target in clinical casework.

Toxicology

Information could not be identified.

Adverse reactions in humans

The total number of cases reported in the scientific literature is very small and the detection of other drugs in published cases has also been reported. Clinical features associated with DOC intoxication included agitation, aggressive behaviour, hallucinations, tachycardia, rhabdomyolysis, seizures, and hyperthermia. In one case, some clinical features were observed to persist for up to 33 h.

Dependence potential

Dependence potential in humans or animals has not been demonstrated.

Abuse potential

Studies specifically linked to DOC could not be identified.

Therapeutic applications / usefulness

DOC is not known to have any therapeutic uses.

Listing on WHO Model List of Essential Medicines

DOC is not listed.

Marketing authorizations

DOC is not known to have any marketing authorisations.

Industrial use

DOC is not known to have any agricultural, industrial or cosmetic uses.

Non-medical use

The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). Household or subpopulation surveys that specifically probe for prevalence of DOC could not be identified. Use of DOC is presumably limited to people who use hallucinogenic drugs in recreational settings (e.g. home environments, outdoors, discotheques/nightclubs and outdoor music festivals) rather than the general population.

Nature and magnitude of public health problems

The information currently available suggests that DOC is most commonly found in the form of blotter papers and that it has also been misrepresented as LSD, which adds to health risks to people who use these substances where information about the identity and/or the dose are unavailable. Some Internet retailers also offer DOC for sale as a research chemical. Information from acute intoxications suggests that some people have obtained access to the powdered form which can increase the risk of overdose and untoward effects.

Licit production, consumption, and international trade

DOC is available as standard reference material and produced for scientific research by commercial suppliers. Other uses could not be identified.

Illicit manufacture and traffic

DOC has been formally notified in Europe in 2004 but its first published synthesis dates back to 1973. In Europe, DOC was encountered in seizures and collected specimens in several countries and notified between 2004–2016. The majority of notifications described the detection of DOC in blotters although powders and liquid samples were also reported. In the period between 2006 and 2009, a number of DOC identifications obtained from seizures (mostly blotters but also some powdered and liquid material) have been published in the forensic literature the United States of America. According to UNODC, a total number of 77 countries have so far reported the detection of DOC.

Current international controls and their impact

DOC is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

Current and past national controls

DOC is controlled in some UN Member States.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Not available.

B. *Chemical Abstract Service (CAS) Registry Number*

42203-77-0 (HCl salt)
123431-31-2 (freebase)
53626-23-6 ((*R*)-isomer HCl salt)
53626-24-7 ((*S*)-isomer HCl salt)
773790-50-4 ((*R*)-isomer freebase)
756418-21-0 ((*S*)-isomer freebase)
1419924-18-7 (1,2,3,4,5,6-¹³C freebase)
1794827-31-8 (2,5-(trideuteromethoxy) HCl salt)
1795121-92-4 (2,5-(trideuteromethoxy) freebase)

C. *Other Chemical Names*

4-Chloro-2,5-dimethoxyamfetamine
2,5-Dimethoxy-4-chloroamfetamine
1-(4-Chloro-2,5-dimethoxyphenyl)propan-2-amine
1-(4-Chloro-2,5-dimethoxyphenyl)-2-propanamine
2-(4-Chloro-2,5-dimethoxy-phenyl)-1-methyl-ethylamine
4-Chloro-2,5-dimethoxyphenylisopropylamine

D. *Trade Names*

Not available.

E. *Street Names*

DOC
3C-C
4-Cl-2,5-DMA
4-Chloro-2,5-DMA

F. *Physical Appearance*

DOC HCl is a white, odorless, and crystalline solid.

G. *WHO Review History*

DOC has not been previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that DOC clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from

literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

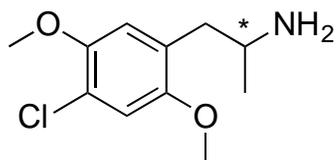
A. Chemical Name

IUPAC Name: 1-(4-Chloro-2,5-dimethoxyphenyl)propan-2-amine

CA Index Name: 4-Chloro-2,5-dimethoxy- α -methyl-benzeneethanamine

B. Chemical Structure

Free base:



Molecular Formula: C₁₁H₁₆ClNO₂

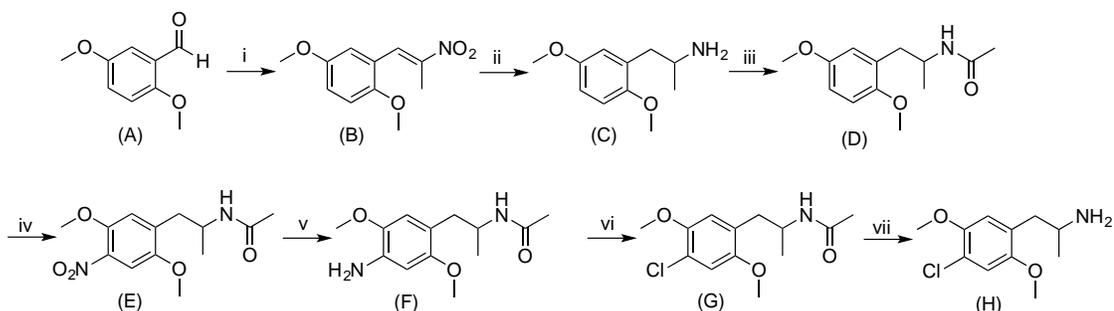
Molecular Weight: 229.70g/mol

C. Stereoisomers

The presence of an asymmetric carbon atom in the α -position (asterisk above) gives rise to the (*R*)- and (*S*)-enantiomer of DOC. On the street level, DOC is most likely available in the racemic form.

D. Methods and Ease of Illicit Manufacturing

Information on the manufacturing of DOC seized or collected from the market is not available. Its preparation is straightforward and follows standard procedures using cheap reagents. One example follows the procedure outlined below which represents the first publication of DOC synthesis in 1973 (1). The procedure used in this approach begins with 2,5-dimethoxybenzaldehyde (A) followed by the Henry reaction to give the nitropropene intermediate (B) and reduction to 2,5-dimethoxyamfetamine (DMA) (C). Protection of the amine leads to *N*-acetyl-DMA (D) that in turn is converted to the nitro analogue (E). The reduced 4-amino-DMA (F) undergoes a Sandmeyer reaction that yields the 4-chloro analogue (G). Deprotection releases the desired DOC product (H) in the racemic form (1). Other examples can be found in Annex 2.



Reagents and conditions: (i) NH₄Ac, nitroethane, AcOH; 100 °C, 3 h (ii) LiAlH₄, Et₂O, reflux, 20 h; (iii) Ac₂O, NaAc, H₂O, shaken until exothermic reaction ceased; (iv) HNO₃, NaNO₂, AcOH, H₂O, rt, 4 h, then cooled; (v) Pd/C, H₂, EtOH, rt, 3 days; (vi) HCl, H₂O, NaNO₂, CuCl; 0 °C–rt, then 70 °C and cooled (vii) NaOH, H₂O, ethylene glycol, reflux, 15 h (1).

E. Chemical Properties

Melting point

HCl: 193–194.5 °C (EtOH/Et₂O) (1)

HCl: 187–188 °C (acetone/EtOH) (2)

HCl: 188–192 °C (EtOH/Et₂O) (3)

Freebase: 95–102 °C (EtOH/Et₂O) (3)

HCl: 194.6 °C (4)

HCl (*S*)-Isomer: 198 °C (acetone/EtOH) (2)

HCl (*R*)-Isomer: 195 °C (acetone/EtOH) (2)

Boiling point

Information could not be identified.

Solubility

Phosphate-buffered saline (pH 7.2) approximately 5 mg/mL (HCl) (5, 6); ~5 mg/mL in ethanol & DMSO and ~10 mg/mL in *N,N*-dimethylformamide (6).

F. Identification and Analysis

Data and analytical methodologies that facilitate the identification of DOC in various sample matrices are available (Annex 2). Analytical reference standards are accessible to assist with the implementation of routine methods of analysis associated with forensic and clinical investigations. Analysis of biological specimen might require the implementation of sensitive techniques in cases where low concentrations are involved due to the potency of this substance. Typically, the parent molecule is used as the analytical target and it has been observed that various immunoanalysis assays developed for detecting amphetamine and methamphetamine-type drugs might not be able to generate a positive finding for DOC (7-12) due to lack of sufficient cross-reactivity (exception: 33% in one particular amphetamine test kit (13)), thus, potentially leading to false negative findings when relying on such routine methods alone. It is most likely that collected and seized material will represent the racemic mixture rather than a specific

enantiomer. The differentiation between the two enantiomers might present challenges in routine forensic laboratories unless more specific approaches are employed to facilitate chiral analysis.

3. Ease of Convertibility Into Controlled Substances

No information could be identified. Although it appears that a dehalogenation of DOC specifically has not been published, a variety of reductive dehalogenation methods exist that might be able to facilitate the removal for the chloro substituent (14, 15). Whether or not the amine would have to be protected for such a reaction has not been investigated. This dehalogenated intermediate (i.e. 2,5-dimethoxyamphetamine, intermediate C (DMA), Section D) might then be available for bromination to give DOB (2, 16). The dehalogenation of DOC to DMA however would already constitute a conversion to a controlled substance since it is also listed in Schedule I of the 1971 UN Convention on Psychotropic Substances. A conversion of DOC to DOM has also not been investigated but examples exist that describe a bromine to methyl conversion (17). The methylation would however require *N*-protection. Overall, it might not be practical to consider a conversion into another controlled substance such as DMA, DOB or DOM given that these substances can be prepared quite easily using cheap reagents.

4. General Pharmacology

A. *Routes of administration and dosage*

DOC is most commonly administered orally and/or sublingually when encountered in the form of paper blotters. A typical dose range to induce hallucinogenic effects has been estimated at 1.5–3.0 mg (18-20). Initial self-experiments documented by Shulgin in the early to mid-1970s suggested that DOC was inactive at 0.4 mg and below (21). In the United States of America, DOC has also been seized in the powdered and liquid form (22). The (*R*)-enantiomer of the hallucinogenic analogues DOM, DOB, and DOI have been shown to be more potent than the (*S*)-form and the racemate (18) but whether this extends to DOC remains to be confirmed.

B. *Pharmacokinetics*

In humans, hallucinogenic and other psychoactive effects have been reported to last between 12–24 h (18) and it is conceivable that further after effects might be experienced (depending on dose) beyond that time point. The analysis of rat urine (male Wistar) by gas chromatography mass spectrometry following administration by gastric incubation revealed the detection of the two *O*-demethylated (2- and 5-position) metabolites that also underwent conjugation to glucuronides or sulfates (23). This main metabolic step was found to be catalysed by CYP2D6 in an *in vitro* assay that employed baculovirus-infected insect cell microsomes. Furthermore, DOC was found to function as a non-mechanism-based competitive CYP2D6 inhibitor (24).

C. Pharmacodynamics

The number of detailed pharmacological studies associated with DOC is comparatively limited. However, the available evidence suggest that it shares the pharmacological key features also observed with other classical (serotonergic) hallucinogenic analogues such as DOI, DOM, and DOB (18, 25, 26). DOC acts as a 5-HT_{2A} receptor agonist with high affinity (Table 1), a key element in mediating the hallucinogenic effects in humans (27-30). The iodo analog (*R*)-DOI has emerged as a potent anti-inflammatory agent mediated by 5-HT_{2A} activity (31) but whether this extends to closely related analogues such as DOC remains to be investigated. (*R*)-DOI is also widely used as a radioligand for studies involving 5-HT₂ receptor subtypes.

Table 1. DOC <i>in vitro</i> data ^a	Reference
<u>Binding to 5-HT₂ receptors ^b</u> DOC (K _i = 218 nM), DOB (K _i = 41 nM), DOI (K _i = 19 nM), DOM (K _i = 100 nM)	(32, 33)
<u>Binding to h5-HT_{2A/2B/2C} receptors ^c</u> h5-HT _{2A} : DOC (K _i = 1.4 nM), DOB (K _i = 0.6 nM), DOI (K _i = 0.7 nM) h5-HT _{2B} : DOC (K _i = 31.8 nM), DOB (K _i = 26.9 nM), DOI (K _i = 20.0 nM) h5-HT _{2C} : DOC (K _i = 2.0 nM), DOB (K _i = 1.3 nM), DOI (K _i = 2.4 nM) r5-HT _{2B} : DOC (K _i = 26.8 nM), DOB (K _i = 21.8 nM), DOI (K _i = 26.6 nM)	(34)
<u>Binding to h5-HT_{1A} and D₂ dopamine receptors ^d</u> r5-HT _{1A} : DOC (K _i = 4520 nM), DOB (K _i = 4280 nM), DOI (K _i = 3175 nM) hD ₂ : DOC (K _i >10,000 nM), DOB (K _i >10,000 nM), DOI (K _i >10,000 nM)	(35)
<u>Binding to h5-HT_{1A} and 5-HT_{2A/2C} receptors ^e</u> h5-HT _{1A} : DOC (K _i >9,200 nM), LSD (K _i = 2.5 nM) h5-HT _{2A} : DOC (K _i = 4 nM), LSD (K _i = 0.47 nM) h5-HT _{2C} : DOC (K _i = 3.57 nM), LSD (K _i = 3.22 nM) DOC did not bind to dopamine and serotonin transporters (HEK-hDAT and HEK-hSERT cells) with K _i below 10,000 nM; K _i DOC at HEK-hNET = 7,700 nM	(36)

<p><u>Functional activity</u>^f</p> <p>h5HT_{1A} [³⁵S]GTPγS binding: DOC (EC₅₀ > 10,000 nM and minimal activity as 5-HT_{1A} antagonist using inhibition of WAY-100,635 (5-HT_{1A} antagonist); LSD (EC₅₀ = 6.4 nM)</p> <p>h5HT_{2A} [³H]arachidonic acid (AA) release: DOC (EC₅₀ = 2.91 nM); LSD (EC₅₀ = 1.01 nM)</p> <p>h5HT_{2A} IP-1 formation: DOC (EC₅₀ = 1.5 nM; E_{max} = 102.4%); LSD (EC₅₀ = 0.264 nM; E_{max} = 80.3%)</p> <p>h5HT_{2C} IP formation: DOC (EC₅₀ = 14.6 nM; E_{max} = 97%); LSD (EC₅₀ = 1.14 nM; E_{max} = 74.6%)</p>	(36)
<p>^a As of July 2019.</p> <p>^b Radioligand [³H]ketanserin (antagonist) (K_i = 1.2 nM); rat frontal cortex.</p> <p>^c Radioligand [³H]DOI for 5-HT_{2A/2C} and [³H]5-HT for 5-HT_{2B}; membranes for radioligand binding assays prepared from suspension-grown AV12 cells (Syrian hamster fibroblasts) stably transformed with human 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C} receptors. Cloned rat 5HT_{2B} also used.</p> <p>^d Radioligand [³H]8-OH-DPAT for 5-HT_{1A} and [³H]<i>N</i>-methylspiperone for D₂ receptor; rat 5-HT_{1A} expressed in CHO cells.</p> <p>^e Radioligand [³H]8-OH-DPAT for 5-HT_{1A} and [³H]DOI for 5-HT_{2A/2C}; HEK-h5HT_{1A}, HEK-h5HT_{2A}, HEK-h5HT_{2C}.</p> <p>^f h5HT_{1A} [³⁵S]GTPγS binding to G proteins using HEK-5HT_{1A} cells; dose-response curve with full agonist serotonin conducted to identify full and partial agonist compounds; [³H]arachidonic acid release using HEK-5-HT_{2A} cells; inositol-1-phosphate (IP-1) accumulation. Activation of 5-HT_{2A} receptors by measuring accumulation of inositol mono- phosphate using an IP-1 Elisa kit; stimulated IP-1 formation normalised to the maximal effect of serotonin (100%).</p>	

Existing animal data (Table 2) indicate that the potency of DOC is comparable to DOB and DOI and that it fully substituted for the discriminative stimulus effects of DOM, LSD, and DMT (*N,N*-dimethyltryptamine, with the latter depending on the time point tested) (36).

Table 2. DOC <i>in vivo</i> animal data ^a	Reference
	(1)

<p><u>Assessment of potency in rats</u> ^b</p> <p>DOC found to be equipotent with DOM and DOB in male rats (10 mg/kg, p.o.) to induce hypersalivation, papillary dilation, retraction of scrotum, loss of orientation reflexes, analgesia, hypomotility, and walking with a slinking gait</p>	
<p><u>Assessment of potency in rabbits (hyperthermia)</u> ^c</p> <p>DOC (0.12 µmol/kg): 80 min to peak effect; mean rise in temp = 1.40 °C; integrated temp (0–240 min) = 250 °C; approx. dose for 1 °C rise = 0.053 µmol/kg; potency rel. to DOM = 3.77 (a) and 3.91 (b)</p> <p>DOB (0.1 µmol/kg): 100 min to peak effect; mean rise in temp = 1.45 °C; integrated temp (0–240 min) = 240 °C; approx. dose for 1 °C rise = 0.049 µmol/kg; potency rel. to DOM = 4.05 (a) and 3.01 (b)</p> <p>DOM (0.5 µmol/kg): 120 min to peak effect; mean rise in temp = 1.43 °C; integrated temp (0–240 min) = 271 °C; approx. dose for 1 °C rise = 0.2 µmol/kg; potency rel. to DOM = 1.00 (a) and 1.00 (b)</p> <p>LSD was 33- and 31.7-times more potent than DOM; a dose of 0.0061 µmol/kg produced a 1 °C rise</p> <p>Assessment of potency in cats (EEG) ^d</p> <p>DOC (between 0.24 and 0.48 µmol/kg, i.m.); pupils less than 25% dilated DOB (between 0.2 and 0.4 µmol/kg, i.m.); pupils less than 25% dilated DOM (between 1 and 2 µmol/kg, i.m.); pupils less than 25% dilated LSD (between 0.05 and 0.1 µmol/kg, i.m.); pupils less than 25% dilated</p>	(2)
<p>The relative potency in the hyperthermia model of rabbits was listed as 1000 (LSD), 114 (DOC) and 123 for DOB</p>	(37)
<p><u>Locomotor activity in mice</u> ^e</p> <p>Time- and dose-dependent depression of locomotor activity following 3 and 10 mg/kg DOC occurred within 10 min following injection and lasted 30–80 min. DOC also produced stimulant effects</p>	(36)
<p><u>Stimulus generalisation in drug discrimination studies</u> ^f</p> <p>DOC substituted for DOM-trained rats, e.g. close to 100% at 0.7 mg/kg (i.m)</p>	(32)
	(36)

<p><u>Stimulus generalisation in drug discrimination studies</u>^g</p> <p>At 15 min: DOC fully substituted for DOM (ED₅₀ = 0.13 mg/kg) and LSD (ED₅₀ = 0.39 mg/kg). DOC produced 65 % DMT appropriate responding (1 mg/kg), and <50 % drug-appropriate responding in MDMA- and methamphetamine-trained rats. Response rate decreased following 2.5 mg/kg DOC. Rats failed to respond, and decreased muscle tone was observed in 12/24 rats.</p> <p>At 60 min: DOC fully substituted for DMT (ED₅₀ = 0.61 mg/kg), DOM (ED₅₀ = 0.26), and LSD (ED₅₀ = 0.23). In MDMA-trained rats, DOC produced 60% drug-appropriate responding (1 mg/kg), and none for methamphetamine at any dose. Doses of 1 mg/kg and higher decreased the response rates in rats. Substantial rate suppression and failure to complete the first fixed ratio were observed following 2.5 mg/kg DOC in MDMA-trained rats (4/6 rats) and 5 mg/kg in methamphetamine-trained rats (5/6 rats).</p>	
<p><u>Open field test. Compounds showing LSD-like effects</u>^h</p> <p>DOC (0.75 µmol/kg), DOB (0.064 µmol/kg), LSD (0.11 µmol/kg)</p>	(2)
<p><u>Conditioned place preference (CPP)</u>ⁱ</p> <p>Mice conditioned with DOC (0.3 and 0.5 mg/kg) exhibited significantly increased place preference, when comparing the time spent in the drug paired compartment between the pre- and post-conditioning phases. DOC was stated to show aversive effects in the CPP at higher doses though it was unclear whether other reasons might have accounted for a reduced CPP at higher doses compared to intermediate doses.</p> <p><u>Self-administration in rats</u>^j</p> <p>Number of infusions and active lever presses for DOC (0.01 mg/(kg/infusion)) not significantly different compared to the vehicle-treated group. The number of active lever presses (same dose) did also not increase significantly when assessing days 1–7 individually. However, an assessment of mean numbers of infusions and lever presses (during days 5–7) was considered significant without further details.</p>	(38)
<p>^a As of July 2019.</p> <p>^b DOM: 1-(2,5-dimethoxy-4-methylphenyl)propan-2-amine; DOB: 1-(4-bromo-2,5-dimethoxyphenyl)propan-2-amine.</p>	

^c Measurement of rectal temperature in Old English rabbits; potency expressed relative to DOM (a. max increase in temperature at particular does level, b: integrated area under time curve; approximate dose for 1 °C rise in temp also determined for comparison with DOM). Three different doses were tested per drug but results of only one test dose given in table above. Drugs were administered into rabbits by injection into a marginal ear vein.

^d Electrodes implanted in cats over lateral and suprasylvian gyri of cerebral cortex; drugs administered intramuscularly; when drugs produced hypersynchronous 4–6 Hz activity in EEG, an auditory stimulus of 1000 Hz 80 dB was presented; this stimulus elicited a standard behavioural response: cats opened eyes wide and raised or turned head toward source of sound; this standard behavioral response was accompanied by full synchronization (low amplitude, high frequency activity) in the EEG. At certain levels the 4–6 Hz activity reappeared after stimulus was switched off (“phasic” EEG response). Dose required to elicit phasic EEG response between the bursts of hypersynchronous 4–6 Hz activity was determined.

^e Separate groups of 8 male Sprague-Dawley rats (0.1, 0.3, 1, 3, and 10mg/kg, i.p.). Horizontal activity (interruption of photocell beams) measured for 8 h within 10-min periods, beginning at 0800 (2 h after lights on).

^f No details given in this book chapter.

^g Two-lever choice methodology, separate groups comprising 15 to 32 male Sprague-Dawley rats trained to discriminate one of the five compounds from saline: methamphetamine (1 mg/kg), MDMA (1.5 mg/kg), LSD (0.1 mg/kg), DOM (0.5 mg/kg), and DMT (5 mg/kg) (all i.p. administration). Food available under FR 10 schedule of reinforcement. Compounds tested 15 min after i.p. injection; DOC was tested at two time points, 15 and 60 min, which corresponded with the peak depressant and peak stimulant locomotor activity effects. In contrast with training sessions, both levers active, such that ten consecutive responses on either lever led to reinforcement.

^h Open-field apparatus with circular arena (diameter 82 cm) illuminated by 4 x 150 W lamps with background white noise level of 88 dB. LSD injected 15 min before testing but all other test drugs administered subcutaneously to groups of eight rats 1.5–3 h before animals were placed in the open field for a 3 min test period. Rats scored according to the number of times they reared, preened, and defaecated, the number of faecal boluses passed, the number of floor squares traversed at the periphery, and, separately, the number of squares traversed in the central part of the field. Doses quoted are the lowest at which significant effects were detected.

ⁱ C57BL/6 mice (i.p. injections) of vehicle or either of three doses of DOC (0.1, 0.3, and 0.5 mg/kg) after the procedures were confirmed with methamphetamine (1 mg/kg). Unbiased method was used.

^j Male Sprague-Dawley rats; testing procedure: two response levers; pressing right lever resulted in the delivery drug solution for 6 s (fixed ratio [FR] 1 schedule). During injection, a stimulus light above active lever was illuminated, and light stayed illuminated throughout the time-out period (20 s) that followed each injection. Pressing the left lever had no programmed consequences, but the number of presses was counted. Daily test sessions lasted 2 h, and the experiment was continued for 7 consecutive days. Training: rats trained to press a lever to obtain 45 mg of food pellets until desired criteria had been achieved (100 food pellets over 3 consecutive days) in a 3 h daily session. Maximum training period was 7 days, and the successfully trained rats elected for further tests.

5. Toxicology

No information could be identified.

6. Adverse Reactions in Humans

Reports associated with the detection of DOC in biofluids taken from cases of intoxication is summarised in Table 3. The total number of cases reported in the scientific literature is small and the detection of other drugs has also been reported. Clinical features associated with DOC intoxication included agitation, aggressive behavior, hallucinations, tachycardia, rhabdomyolysis, seizures, and hyperthermia. In a report provided by the UNODC that includes data obtained from the UNODC's ToxPortal, two post-mortem cases (one in 2015 and one in 2018) have been described that feature the detection of DOC. One of those was described as a poly-drug case but details were not provided (39).

Year ^b	Cases	Patient, age	Comments (examples)	Reference
Non-fatal intoxications				
2008	1	M, 20	Collapsed having tonic-clonic seizures at a rave party. At arrival at hospital: Glasgow Coma Scale of 3/15; sinus tachycardia with HR of 152 beats/min and BP of 144/57 mmHg. T 36.8 °C; both pupils dilated (6 mm) and nonreactive to light; neurological examination normal, normal tone and reflexes and no evidence of clonus. Metabolic acidosis (thought to be linked to his tonic-clonic seizures before admission) and biochemical evidence of rhabdomyolysis. Patient admitted to ingestion of MDMA and what he believed was DOI.	(40)

			Serum and urine analysis revealed detection of DOC, MDMA (0.57 mg/L) and MDA (<0.05 mg/L). Blotters impregnated with DOC recovered from other attendees of rave.	
2014	2	M, 17	<p>Medical attention needed 4 h after ingestion of a white powder believed to be DOC. One patient presented with generalised tonic-clonic seizure; on arrival at hospital HR 108; BP 131/54; T 38.5 °C; dilated pupils, agonal respirations, and a Glasgow Coma Score of 7 (E2M1V4); course complicated by agitation and hyperthermia requiring sedation, paralysis and external cooling, rhabdomyolysis and aspiration pneumonia. Extubated on day 2.</p> <p>Urine toxicology showed benzodiazepines and THC and DOC detected in urine and serum.</p> <p>Other patient described sense of euphoria and clarity and without complaints; pupils were 8 mm and reactive; BP 152/89, HR 113, RR 28; afebrile. Endorsed ingesting ~2 mg; used 4 times in previous 2 weeks without adverse effects.</p>	(41)
2015	1	M, 18	<p>Man with history of migraines and a single febrile seizure at age 2 presented to the emergency department in status epilepticus; came home with agitation and hallucinations. Patient believed to have taken LSD and marijuana; patient found to be seizing with left gaze deviation, dilated pupils, and abnormal movements of all extremities. Tachycardia and tachypnea (BP 132/66, HR 125, T 37.3 °C, respiratory rate 24, oxygen saturation 95%); initial ECG showed sinus tachycardia with a prolonged QT interval (PR 176 milliseconds, QRS 94 milliseconds, QTc 492 milliseconds). On arrival to hospital, still having tonic head turning and gaze deviation, with improvement in the tonic head movement with 2 mg of intravenous (i.v.) lorazepam. Initial laboratory test results notable for an anion gap metabolic lactic acidosis, profound leukocytosis, evidence of early rhabdomyolysis and hyperglycemia but otherwise normal electrolytes, and a negative troponin. Head computed tomography on arrival showed subtle hypodensities in the bilateral cerebellum and occipital lobes suggestive of posterior reversible encephalopathy syndrome. He was successfully extubated on hospital day 2 with amnesia for the event and mental status difficulties but an otherwise normal neurologic examination.</p>	(11)

			Urine toxicology positive for benzodiazepines (treatment), opioids and cannabinoids. DOC serum concentration detected at 3 ng/mL approx. 5.5 h after ingestion.	
2015	6	M, 23–27	<p>Six males presented at hospital 2 h after ingesting a drug different from their usual drug. All displayed a range of symptoms: severe agitation and extreme aggressive behavior (n = 6), delirium (n = 6), hallucinations (n = 6), mydriasis (n = 6), tachycardia (n = 6) with a HR between 120 and 160 bpm and fever (n = 4) with a temperature between 38 and 39 °C. Four of them developed rhabdomyolysis. All discharged after 12 to 72 hours.</p> <p>EMIT urine toxicology positive for amphetamine (n = 6), cannabis (n = 3) and opioids (n = 1). Urine analysis by GC-MS confirmed detection of DOC in all cases.</p>	(42)
2016	1	M, NR ^c	<p>Patient presented with visual hallucinations, euphoria, altered mental status, tachycardia of HR = 128, T 38.1 °C. Four h into the visit (roughly 21 h after ingestion) still symptomatic (tachycardia and fever however resolved by then).</p> <p>Patient confirmed taking DOC blotter, which was confirmed in blood and urine; also positive for THC. Symptom duration reported to be 33 h.</p>	(43)
2017	1	M, 18	<p>Patient presented with seizures, agitation and hallucinations following the consumption of what was believed to be one LSD blotters and MDMA at rave party; incoherent speech, mydriasis; BP 130/50mmHg and HR 84. Poisoning severity score (PSS) calculated at 6 h after consumption was 2. Patient was discharged on the next day.</p> <p>Blood and urine samples obtained approx.. 6 h after ingestion. Plasma: DOC (10 µg/L), MDMA (190 µg/L), MDA (14 µg/L); urine: DOC (1300 µg/L), MDMA (50 µg/L), MDA (2.2 µg/L). LSD was not detected.</p>	(44)
2017	1	M, 21	<p>Patient presented with agitation and hallucinations following the consumption of what was believed to be 1.5 LSD blotters (same rave party, above); tachycardia (HR 135 beats/min), bilateral mydriasis, BP 133/74 mmHg. PSS = 2 at 8 h after ingestion.</p>	(44)

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			Blood and urine samples obtained approx. 8 h after ingestion. Plasma: DOC (13 µg/L); urine: DOC (720 µg/L), MDMA (0.05 µg/L), MDA (0.02 µg/L); blood ethanol 0.13 g/L; LSD was not detected.	
2017	1	M, 21	<p>Patient presented with agitation and hallucinations following the consumption of what was believed to be alcohol, ketamine, cocaine, cannabis and LSD during a rave party; visual hallucinations (at 24 h), BP 120/80mmHg, HR = 93 beats/min. PSS = 2 at the 11 h time point.</p> <p>Blood and urine samples obtained approx..11 h after ingestion. Plasma: DOC (<10 µg/L), cocaine and benzoylecgonine (175 µg/L), methylecgonine (14 µg/L), ketamine (100 µg/L), norketamine (250 µg/L); urine: DOC (320 µg/L), BECG (16.5 µg/L), MECG (4.9 µg/L), ketamine (9 µg/L), norketamine (7 µg/L); blood ethanol 1.28 g/L; cannabis positive, LSD was not detected.</p>	(44)
2017	1	M, 16	<p>Patient presented with “near death experience” and serious anxiety following consumption of two blotters; hallucinations and bilateral mydriasis with PSS = 2 at the 4 h point after consumption.</p> <p>Blood and urine samples obtained approx. 4 h after ingestion. Plasma: DOC (<10 µg/L); urine: DOC (300 µg/L), cannabis positive.</p>	(44)
2017	1	M, 21	<p>Patient presented with seizures following ingestion of “LSD derivative” bought on Internet; hyperthermia (39.5 °C), tachycardia (HR 150 beats/min), mydriasis, BP 150/80 mmHg, PSS = 3 at 5 h after ingestion. Management required intubation and ventilation.</p> <p>Blood and urine samples obtained approx. 5 h after ingestion. Plasma: DOC (18 µg/L), methiopropamine (430 µg/L), pentedrone (35 µg/L); urine: DOC (470 µg/L), methiopropamine (12.6 µg/L), pentedrone (1.12 µg/L), alpha-methyltryptamine (0.5 µg/L), methadone (0.22 µg/L), free morphine (24 µg/L), codeine (5µg/L).</p>	(44)
Fatal intoxications				
2014	1	M, 37	Known user of methamphetamine found dead at home and a collection of other new psychoactive substances found at the	(9)

		<p>scene. Findings at autopsy included pulmonary edema and a subgaleal hemorrhage on the right parietal scalp.</p> <p>Quantitative analyses showed DOC at 377 ng/mL in iliac blood, 3,193 ng/mL in urine, 3,143 ng/g in liver and 683 ng/g in brain. DOC was not detected in the gastric contents of the decedent and no other drugs were detected. Cause of death ruled accidental due to DOC intoxication.</p>	
<p>^a As of July 2019.</p> <p>^b Refers to year published.</p> <p>^c Age not reported.</p>			

7. Dependence Potential

A. *Animal Studies*

Information could not be identified.

B. *Human Studies*

Information could not be identified.

8. Abuse Potential

A. *Animal Studies*

Drug discrimination data (Table 2) indicate that DOC produces stimulus effects in rats similar to related serotonergic hallucinogens such as DOM, LSD and DMT when tested at two time points (peak depressant effect after 15 min and peak stimulant locomotor activity effects at 60 min mark) (36). This was consistent with previous observations where DOC was reported to show DOM-like stimulus effects in rats (32). One recent preliminary study suggested that DOC might show some reinforcing properties in rats under certain conditions (Table 2) and further studies are warranted to investigate this further. The rates of decline of lever pressing and their terminal levels maintained by DOC and vehicle were similar following their substitution for food, and DOC infusion nonspecifically increased the ratio of DOC to vehicle inactive lever pressing similarly to that on the active lever. Serotonergic hallucinogens are normally not known to be effective in initiating or maintaining self-administration (45) although some test subjects (rhesus monkeys) were observed to display a pattern of transient self-administration where DMT, mescaline and psilocybin (but not DOI) was available (46).

B. *Human Studies*

No information could be identified.

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

DOC is not known to have any therapeutic applications.

10. Listing on the WHO Model List of Essential Medicines

DOC is not listed on the WHO Model List of Essential Medicines.

11. Marketing Authorizations (as a Medicinal Product)

DOC is not marketed as a medicinal product

12. Industrial Use

DOC has no reported industrial use.

13. Non-Medical Use, Abuse and Dependence

Household or subpopulation surveys that specifically probe for prevalence of DOC could not be identified in the currently available literature. Epidemiological data, such as prevalence of use, abuse and dependence information, are not available specifically for DOC. However, the Monitoring the Future (MTF), a national cross-sectional survey in the United States of America (USA) that queries use of hallucinogens and LSD in particular among high-school attending adolescents revealed that substance use remained relatively stable (47). The mode of use may involve the combinational use (intentionally or unintentionally) of other drugs and users may be unaware of the exact dose or compound being ingested (by whatever route). Dependence-producing properties in humans have not been studied but is unlikely to result in dependence similar to other serotonergic hallucinogens such as LSD or psilocybin. Although it is likely that some people who use hallucinogens such as LSD will also be likely to consider using closely related lysergamide-based new psychoactive substances such as 1-propanoyl-LSD and perhaps also other phenylethylamine-based NPS (48, 49) it is unknown whether this would extend to hallucinogenic amfetamines such as DOC if users are given the choice. Use of DOC is presumably limited to recreational substance users and psychonauts rather than the general population.

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

DOC is offered for sale by some Internet retailers as a substance in its own right which means that some users may be exposed intentionally whereas others may be exposed unintentionally after consuming a product with no indication that it contains this substance or following its ingestion as a component of other substances. Use of DOC is presumably limited to people who use hallucinogenic drugs in recreational settings (e.g. home environments, outdoors, discotheques/nightclubs and outdoor music festivals) rather than the general population. The information currently available suggests that DOC is most commonly found in the form of blotter papers and that it has also been misrepresented as

LSD (50, 51) (and Section 16). For example, the analysis of results obtained by a Spanish drug-testing organisation revealed that in the period January 2009 and February 2015, 41 out of 18,222 tested samples (0.23%) contained DOC. Seventeen out of these 41 were handled (i.e. represented) as LSD (52). It is conceivable that DOC might be also supplied/sold as a “legal” replacement for LSD in countries that do not control this substance but further studies are needed to confirm this. Ingestion of DOC has been associated with a range of clinical features that will likely lead to impaired driving and potentially aggressive behaviour. The analysis of samples submitted for analysis by patients as part of the Swedish STRIDA project during the period 2010–2015 showed that one powdered sample identified as DOC was received in 2012 (53).

15. Licit Production, Consumption and International Trade

DOC is available as standard reference material and produced for scientific research by a number of commercial suppliers. Other uses could not be identified.

16. Illicit Manufacture and Traffic and Related Information

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) received reports that DOC (identification notified in February 2004 but detected in the reporting country first in 2001) was encountered in seizures and collected specimens in Sweden, United Kingdom, France, Norway, Italy, Belgium, Ireland, Slovenia, Spain, Croatia, Denmark, Czech Republic, Luxembourg, and Latvia. The notifications were received between 2004–2016 and the majority of notifications described the detection of DOC in blotters although powders and liquid samples were also reported (54). The Hungarian Institute for Forensic Sciences was cited to confirm confiscation of DOC (among other substances) during 2011–2013 (55).

In the period between 2006 and 2009, a number of DOC identifications obtained from seizures (mostly blotters but also some powdered and liquid material) have been published by the United States Drug Enforcement Administration (22, 23).

Detections of DOC have also been reported to UNODC’s Early Warning Advisory on New Psychoactive Substances (56). Detections of DOC were reported by the following number of countries (period 2013–2016 contains multiple entries for some countries): 2009: 2; 2010: 2; 2011: 2; 2012: 1; 2013: 41; 2014: 29; 2015: 40; 2016: 30; 2017: 17; 2018: 4. In a recent UNODC communication to the ECDD secretariat, the number of reporting countries stated was 77. UNODC’s evaluation of NPS emergence data (2015–2018) revealed the detection of 78 reports from a total number of 40 countries. Thirty-two reports in 2015; 2016: 32; 2017: 3. Between 2015 and 2017, a total number of 8 countries reported the detection of DOC in blotter, tablet and what appeared to be powdered form (39). UNODC’s evaluation of seizure data (2015–2017) indicate that DOC was encountered in two countries in 2015 and 2017 (2015: “131 units” and “8 doses”; 2017: “1329 tablets” and “2.44 g”) (39).

17. Current International Controls and Their Impact

DOC is not controlled under the 1961 (as amended by the 1972 Protocol), 1971 or 1988 United Nation Conventions.

18. Current and Past National Controls

Refer to Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

No further comments.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances

Annex 2: Investigations associated with the synthesis and chemical analysis of DOC (amongst other substances) including those reported in the published scientific literature

Techniques ^{a,b}	Comment	Reference
MP, EA, IR,	Synthesis of various analogues and pharmacological testing in rats	(1)
MP, EA	Synthesis of various analogues (and DOC enantiomers) and pharmacological testing in animals	(2)
NMR, GC-MS	Analysis of seized sample	(3)
NR	Synthesis of various analogues (not reported for DOC) for receptor binding studies	(4)
NR	Synthesis of various analogues for clinical studies	(5)
NR	Synthesis of various analogues for receptor binding studies	(6)
NR	Synthesis of various analogues for receptor binding studies	(7)
MP, EI-MS, NMR, IR, UV	Synthesis and analytical characterisation	(8)
CE-ESI-MS	Analysis of spiked urine samples	(9)
CE-DAD	Analysis of rat blood following intraperitoneal administration	(10)
EI-, ESI-MS, UV, NMR	Analysis of collected samples	(11)
GC-MS	Metabolism study in rats and urine analysis	(12)
GC-MS, LC-MS	<i>In vitro</i> metabolism studies and identification of cytochrome P450 isoenzymes	(13)
GC-MS	Analysis of biological specimens (non-fatal intoxication)	(14)
GC-MS, LC-DAD	Analysis of collected samples	(15)
GC-MS	DOC included in drug panel for designer drug screen	(16)
LC-MECD	Method development and analysis of collected samples	(17)
GC-(EI/CI)-MS, IR, NMR	Analytical characterisation	(18)
IA, GC-MS	Evaluation of cross-reactivity using immunoassays in urine specimens	(19)
LC-MS	DOC included in analysis of spiked urine and application to clinical samples	(20)
CE	Synthesis and chiral analysis using modified β -cyclodextrins	(21)
NR	Synthesis of various [¹³ C ₆]analogues	(22, 23)
LC-MS, IA	Analysis of spiked biological specimens	(24)
IA	Evaluation of cross-reactivity in spiked urine using immunoassays	(25)
GC-MS	Analysis of biological specimens (fatal intoxication)	(26)
TLC, GC-MS	Analysis of collected samples	(27)
LC-MS	Analysis of biological specimens (non-fatal intoxication)	(28)
LC-MS	Analysis of spiked urine and application to casework samples	(29)
IA	Synthesis and evaluation of cross-reactivity in spiked urine using immunoassays	(30)

IA	Synthesis and evaluation of cross-reactivity in spiked oral fluid using immunoassays	(31)
MP, NMR, GC-MS, IR	Analysis of reference material	(32)
LC-MS	Analysis of biological specimens (non-fatal intoxication)	(33)
GC-MS	Analysis of biological specimens (non-fatal intoxications)	(34)
LC-MS	Analysis of spiked urine and application to casework samples	(35)
TLC, GC-MS	Analysis of collected samples	(36)
GC-MS	Analysis of biological specimens obtained from casework	(37)
GC-MS	Included in analysis of blood samples obtained from casework	(38)
GC-MS, IR	Analysis of reference material	(39)
PSI-and ESI-MS	Analysis of blotter samples	(40)
GC-MS	Analysis of reference material	(41)
LC-MS	Analysis of biological specimens (non-fatal intoxication)	(42)
IA	Synthesis and evaluation of cross-reactivity in spiked blood, urine, and oral fluid using immunoassays	(43)
GC-MS	Analysis of blotter papers	(44)
GC-MS, LC-DAD, LC-MS	Analysis of biological specimens (non-fatal intoxications)	(45)
TLC, GC-MS	Analysis of collected samples	(46)
LC-MS	Analysis of spiked urine and application to clinical samples	(47)
LC-MS	Analysis of collected samples and biological specimens obtained from clinical casework	(48)
NMR	Analysis of collected samples	(49)
CE-DAD	Chiral analysis of collected samples	(50)
LC-UV	Chiral analysis of collected/seized/synthesised samples	(51)
LC-MS	Analysis of biological specimens (fatal intoxication)	(52)
IMS, LC-MS	Analysis of spiked oral fluid	(53)

^a As of July 2019.

^b MP: melting point; EA: elemental analysis; IR: infrared spectroscopy; NMR: nuclear magnetic resonance spectroscopy; GC: gas chromatography; MS: mass spectrometry (may involve high or low resolution approaches); NR: details not reported; EI: electron ionisation; UV: ultraviolet spectroscopy; CE: capillary electrophoresis; ESI: electrospray ionisation; DAD: diode array detection; LC: liquid chromatography (various forms); MECD: multi-channel electrochemical detection; CI: chemical ionisation; IA: immunoanalysis; TLC: thin-layer chromatography; PSI: paper spray ionisation; IMS: ion mobility spectrometry.

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