

Dextromethorphan Pre-Review Report

**Expert Committee on Drug Dependence
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**World Health
Organization**

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Summary

Dextromethorphan (DXM) is an antitussive drug. It is one of the active ingredients in many over-the-counter cold and cough medicines, including generic labels. Dextromethorphan has also found other uses in medicine, ranging from pain relief to psychological applications. It is sold in syrup, tablet, spray, and lozenge forms. In its pure form, dextromethorphan occurs as a white powder.

Dextromethorphan is also used recreationally. When exceeding label-specified maximum dosages, dextromethorphan acts as a dissociative hallucinogen. Its mechanism of action is as an NMDA receptor antagonist, producing effects similar to those of ketamine and phencyclidine (PCP).

Dextromethorphan produces a range of toxicities depending upon either the dose or the components of the specific formulation that was ingested. Cases of recreational abuse of dextromethorphan have been reported in United States, Sweden, Australia, Germany, and Korea primarily among adolescents and young adults. However, these reports are still relatively infrequent.

At the time being, dextromethorphan is not listed in the Schedules of the United Nations 1961 Convention on Narcotic Drugs.

1. Substance identification

A. *International Nonproprietary Name (INN)*

Dextromethorphan

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

125-71-3

125-69-9 (hydrobromide salt)

6700-34-1 (hydrobromide monohydrate)

C. *Other Names*

(±)-3-methoxy-17-methylmorphinan; (+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan; 9a,13a,14a-morphinan, 3-methoxy-17-methyl- (8CI); Ba 2666; d-methorphan.

D. *Trade Names (hydrobromide salt)*

Dextromethorphan is contained in many products such as Acodin® (PL); Akindex® (BE, FR, LU, PL, PT); Argotussin® (PL); Aricodil® (IT); Arpha® (DE); Astho-Med® Husten (CH); Athos (MX); Atuxane® (FR); Babee® Cof Syrup (US); Bechilar® (IT); Benylin® (NL, ZA); Benylin® Antitusivo (ES); Bexin® (CH); Bronchenolo Tosse® (IT); Bronchosedal® (BE, LU); Bronchydex® (FR); Brudex® (MX); Calmerphan® (CH); Calmerphan-L® (CH); Calmesin-Mepha® (CH); Canfodian® (IT); Capsyl® (BE, LU); Cinfatos® (ES); Codotussyl® toux seche (FR); Creomulsion® Cough (US); Creomulsion® for Children (US); Creo-Terpin® (US); Dampo Bij® Droge Hoest (NL); Darolan Hoestprikkeldepend® (NL); Daromefan® (NL); Dekstrometorfaani® (FI); Delsym® (IE, US); Destrometorfano Bromidrato® (IT); Dexatussin® (PL); Dexir® (BE, FR); Dexofan® (DK); Dextphan® (JP); Dextrogel Oral® (CH); Dextromephar® (BE); Dextrométhorphane® (FR); Dextromethorphanum® (LA); Dextrometorfano® (SE); Dextrometorfano® (ES); Dextrometorfano Fabra® (AR); Dextrotos® (AR); ElixSure® Cough (US); Emedrin N® (CH); Fluprim® (IT); Formitrol® (IT); Formulatus® (ES); Hold® DM (US); Humex® (BE, ES); Hustenstillerratiopharm® (DE); Hustep® (JP); Kibon S® (JP); Lagun® (FI); Maximum Strength Cough® (US); Methorcon® (JP); Metorfano® (IT); NeoTussan® (DE, LU); Nodex® (FR); Notuxal® (BE); Nucosef® (AU); Pectofree® (BE); PediaCare® Infants' Long-Acting Cough (US); Pulmoform® (CH); Rami Dextromethorfan Hoestdrank® (NL); Resilar® (FI); Rhinathiol® (FR, LU); Robitussin® (AU, ES, IE, PL, US); Robitussin® CoughGels™ (US); Robitussin® Pediatric Cough (US); Romilar® (AR, BE, ES, LU, MX); Sanabronchiol® (IT); Scot-Tussin DM® Cough Chasers (US); Sebrane® (FR); Siepex® (ES); Silphen DM®; Sisaal® (JP); Soludril Toux seches® (LU); Strepsils® (AU); Tesafilm® (MX); Tip® (ES); Tosfriol® (ES); Tosion retard® (NL); Tossoral® (IT); Touxium Antitussivum® (BE, LU); Triaminic® Thin Strips™ Long Acting Cough (US); Trimpus® (JP); Tusitinas® (ES); Tusorama®

(DE, ES); Tuss Hustenstiller® (DE); Tussal Antitussicom® (PL); Tussidex® (PL); Tussidril® (ES); Tussidril® (PL); Tussinol® (AU); Tussipect® (BE, LU); Tussycalm® (IT); Tuxium® (FR); Valatux® (IT); Valdatos® (ES); Vicks® Hustenpastillen(CH, FR); Vicks® Hustensirup mit Dextromethorphan (CH); Vicks® Tosse Pastiglie (IT); Vicks® Tosse Sedativo (IT); Vicks® Vaposirop (NL); Vicks® Vaposyrup (BE); Vicks® 44 Cough Relief (US); Wick Formel 44 Husten-Pastillen S® (AT, DE); Wick Formel 44 Hustenstiller® (AT, DE); Wick Formula 44 Plus S® (PL); Декстрометорфан® (RU)

E. Street Names

Dextromethorphan has been associated with various street names including “Bromage”; “Brome”; “Candy”; “CCC”; “C-C-C”; “Dex”; “Dextro”; “DM”; “Drex”; “DXM”; “Red Devils”; “Robo”; “Rojo”; “Skittles”; “Triple C”; “Triple C's”; “Tussin”; “Velvet”; “Vitamin D”.

F. Physical properties

As the pure free base, dextromethorphan occurs as an odourless verging on a faint odour, white to slightly yellow crystalline powder.

G. WHO Review History

Several reports suggest misuse of dextromethorphan over the last years, especially in the EU, the United States, Australia and Korea. At the time being, dextromethorphan is not listed in the Schedules of the United Nations 1961 Convention on Narcotic Drugs.

The fourth session of the ECDD in 1953 discussed synthetic substances of morphinan type. To quote from the report published in 1954, ‘The committee considered the evidence on the addiction liability and possible clinical usefulness of dextrorotatory isomer of 3-hydroxy-*N*-methylmorphinan (dextrorphan) and the dextrorotatory isomer of 3-methoxy-*N*-methylmorphinan (dextromethorphan) which is the methyl ether of the former compound. It was concluded that each of these compounds had been demonstrated (1) to have no morphine-like action (2) to lack ability to sustain a morphine addiction, and (3) to have exhibited no signs of addiction liability. Further, although some transformation of dextromethorphan (or dextrorphan) into a product with some analgesic activity is possible, this is sufficiently difficult, and the yield is so small, for it to be regarded as impracticable and to constitute no risk to public health. Therefore, The Expert Committee on Drugs Liable to Produce Addiction Having considered the request of the Swiss Government to have dextrorphan and dextromethorphan exempted from the obligations of the international conventions on narcotic drugs, IS OF THE OPINION that such exemption should be granted in accordance with Chapter 1, Article 3, of the 1948 Protocol, and RECOMMENDS that this opinion be notified to the Secretary- General of the United Nations. The Committee confirmed its opinion, formulated in its third report, that racemorphan, racemethorphan, levorphan, and levomethorphan are addiction-producing substances. It emphasized the probable necessity for special precautionary measures, particularly with respect to the laevorotatory isomers, if

one or another of the dextrorotatory isomers comes into general use in place of codeine, because the procedure for making the dextrorotatory isomer involves the simultaneous production of an equivalent amount of laevorotatory isomer.’

In order to bring more updated and conclusive scientific evidence on the overall risks of dextromethorphan for an eventual international scheduling, a member of the Expert Committee has submitted a proposal to pre-review dextromethorphan at its 35th ECDD.

2. Chemistry

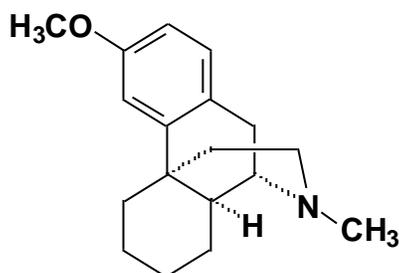
A. Chemical Name

IUPAC Name: (+)-3-methoxy-17-methyl-(9 α ,13 α ,14 α)-morphinan

CA Index Name: (+)-3-methoxy-17-methyl-(9 α ,13 α ,14 α)-morphinan

B. Chemical Structure

Free base:



Molecular Formula: C₁₈H₂₅NO (free base);
C₁₈H₂₆BrNO (hydrobromide salt);
C₁₈H₂₈BrNO₂ (hydrobromide monohydrate)

Molecular Weight: 271.40g/mol (free base);
352.31 g/mol (hydrobromide salt);
370.32 g/mol (hydrobromide monohydrate)

Melting point: 111 °C (free base);
122-124 °C (hydrobromide salt)
116-119 °C (hydrobromide monohydrate)

Boiling point: Decomposes (free base)

Fusion point: n/a

C. Stereoisomers

Dextromethorphan is the dextrorotatory enantiomer of the methyl ether of levorphanol, an opioid analgesic. It is also a stereoisomer of levomethorphan, an opioid analgesic.

D. Synthesis

Dextromethorphan is considered a synthetic opiate. It has been synthesized from a benzyloisoquinoline (with a planar structure) by a process known as Grewe's cyclization (from the 1950's) to give the corresponding morphinan (with a three dimensional structure). The isoquinoline is 1,2,3,4,5,6,7,8-octahydro-1-(4-methoxybenzyl)isoquinoline (there is just one residual double bond at the fusion position of the two rings of the isoquinoline) is converted into the N-formyl derivative, cyclized to the N-formyl normorphinan, and the formyl group reduced to an N-methyl group, to give 3-methoxy-17-methylmorphinan, or Racemethorphan (<http://brainmeta.com/forum/index.php?showtopic=5964>).

E. Chemical description

Dextromethorphan is a synthetic compound. Dextromethorphan is 3 methoxy-17-methylmorphinan monohydrate, which is the d isomer of levophenol, a codeine analogue and opioid analgesic.

F. Chemical properties

Dextromethorphan is freely soluble in ethanol 96% and essentially insoluble in water. Dextromethorphan is commonly available as the monohydrated hydrobromide salt. However, some newer extended-release formulations contain dextromethorphan bound to an ion exchange resin based on polystyrene sulfonic acid. Dextromethorphan's specific rotation in water is + 27.6° (20°C, Sodium D-line).

G. Chemical identification

No information found.

3. Ease of convertibility into controlled substances

Dextromethorphan is not readily converted into controlled substances.

4. General pharmacology**4.1. Pharmacodynamics*****Neuropharmacology and effects on central nervous system***

Dextromethorphan (*d*-3-methoxy-*N*-methylmorphinan) is the *d*-isomer of the codeine analogue methorphan; however, unlike the *l*-isomer, it does not act through opioid receptors. Instead, dextromethorphan binds with high affinity to sites associated with sigma ligands and low affinity to the phencyclidine (PCP) channel of the *N*-methyl-D-aspartate (NMDA) receptor as seen in animal studies. Most NMDA receptors in the brain are thought to be pentameric or tetrameric complexes of the NR1 subunit and one or more of four NR2 subunits (NR2A-2D) (Fig. Kutsuwada et al., 1992). It is of interest to note that dextromethorphan is thought to be NR1/NR2A-containing NMDA receptor –preferred antagonist (Avenet et al., 1997). Conversely, the active metabolite of dextromethorphan,

dextrophan (3-hydroxy-17-methylmorphinan) binds with low affinity to sites associated with sigma ligands and high affinity to the PCP-site (Klein *et al.*, 1989; Murray *et al.*, 1984); (Franklin *et al.*, 1992). The relationship of these receptor binding sites to the pharmacological mechanism of the antitussive effects of dextromethorphan is not known; however, these observations, coupled with the ability of naloxone to antagonize the antitussive effects of codeine but not those of dextromethorphan, indicate that cough suppression can be achieved by a number of different mechanisms.

Behavioural studies in animals

In preclinical rodent and monkey studies, dextromethorphan produces PCP-like stimulus effects in rats and partial substitution for PCP in monkeys. Dextrophan produced full substitution for PCP in both rats and monkeys. Both dextromethorphan and dextrophan produced self-administration in rhesus monkeys trained to previously self-administer PCP (Nicholson *et al.*, 1998). Dextromethorphan can alter self-administration of several drugs of abuse such as morphine, cocaine, and methamphetamine. It attenuates methamphetamine conditioned place preference and behavioral sensitization but has a biphasic effect on cocaine self-administration, locomotor effects and conditioned place preference (Shin *et al.*, 2008).

Interactions with other drugs and medicines

Dextromethorphan should not be taken with monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) because of an apparent serotonin syndrome (fever, hypertension, arrhythmias). Dextromethorphan shouldn't be combined with terfenadine nor with diphenhydramine as life threatening interactions have been reported (Kintz P. und Mangin P. (1992)). Because administration of dextromethorphan can trigger a histamine release, its use in atopic for children is very limited. Additive CNS depressant effects may occur when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

4.2. Routes of administration and dosage

Dextromethorphan, an oral drug, is available as lozenges, capsules, tablets, and cough syrups, in a variety of prescription medications and over-the-counter cough and cold remedies. Products contain dextromethorphan alone or in combination with guaifenesin, brompheniramine, pseudoephedrine, phenylephrine, promethazine, codeine, acetaminophen, and/or chlorpheniramine.

The average adult dose approved of dextromethorphan for antitussive effects is 15-30 mg taken 3 to 4 times per day. It is a highly effective and safe agent in this dose range (Bem *et al.*, 1992).

4.3. Pharmacokinetics

After oral administration, dextromethorphan is quickly absorbed in the gastrointestinal tract with peak serum levels reached within 2-2.5 h. Dextromethorphan is absorbed from the bloodstream and crosses the blood-brain into the cerebral spinal fluid by approximately 33-80 % (Hollander *et al.*, 1994). The antitussive activity of dextromethorphan lasts for approximately 5-6 hours with a plasma half-life of 2-4 hours (Pender *et al.*, 1991).

Dextromethorphan is rapidly metabolized by the liver and is *O*-demethylated to produce its active metabolite dextrorphan. Dextromethorphan is then further *N*-demethylated and partially conjugated with glucuronic acid and sulfate ions (Woodworth *et al.*, 1987). Cytochrome P450 in the 2D6 isoenzyme family inactivates dextromethorphan. Dextromethorphan is eliminated renally unchanged or as a demethylated metabolite. Approximately 5-10 % of people of white European ethnicity lack CYP2D6 which is necessary to demethylate dextromethorphan to dextrorphan. This can lead to acute toxic levels of dextromethorphan when ‘megadoses’ (5-10 times the recommended doses) are given (Motassim *et al.*, 1987). Dextrorphan, the main metabolite, is pharmacologically active with a half-life of approximately 3.5 to 6 h and is a potent NMDA antagonist (Church *et al.*, 1991).

5. Toxicology

Dextromethorphan produces a range of toxicities depending upon either the dose or the components of the specific formulation that was ingested. In 2009, five teenage males died from direct toxic effects of purposeful ingestion of large doses dextromethorphan for recreational purposes in three separate incidents in three states in the USA. The dextromethorphan was obtained from the same internet supplier in each case (Logan *et al.*, 2009). Most cases improve with supportive care alone, but severely intoxicated patients may require significant attention (Boyer, Edward W. 2004). Cases of drivers under the influence of high doses of dextromethorphan displayed symptoms of central nervous system depressant intoxication, and there was gross evidence of impairment in their driving which lead to arrest (Logan, 2009).

6. Adverse reactions in humans

At the recommended doses adverse effects are reported in less than 1% including (Lexi-CompONLINE, 2008):

<i>drowsiness,</i>	<i>nausea,</i>	<i>tachycardia,</i>
<i>dizziness,</i>	<i>gastrointestinal upset,</i>	<i>warm sensations,</i>
<i>coma,</i>	<i>constipation,</i>	<i>inability to concentrate,</i>
<i>respiratory depression</i>	<i>abdominal discomfort</i>	<i>dry mouth and throat</i>

At 5 to 10 times the recommended dose, adverse effects resemble those observed for ketamine or PCP, and these include: confusion, dreamy state, depersonalization, distortion of motor and speech, disorientation, stupor, somnolence, hyperexcitability, ataxia, nystagmus, impaired muscle tone, dissociative anaesthesia, visual hallucinations (closed eye hallucinations of sheets, swirls, and blobs of color), toxic psychosis (Schwartz, 2005; Siu *et al.*, 2007).

When cough and cold preparations that contain dextromethorphan are taken in doses 5 to 10 times the recommended dosage, additive toxicities with the additional ingredients are observed. The combination of dextromethorphan with high doses of guaifenesin causes intense nausea and vomiting; with chlorpheniramine causes flushed skin, mydriasis, tachycardia, delirium, respiratory distress, syncope, and seizures. Acetaminophen toxicity

can also be observed in some preparations containing both dextromethorphan and acetaminophen (Schwartz, 2005).

7. Dependence potential

Little data exists on dextromethorphan dependence besides case studies (e.g., (Miller, 2005)) and anecdotally on one of the many Internet sites devoted to the recreational use of dextromethorphan (e.g., <http://www.third-plateau.org/>). Five cases of confirmed dextromethorphan dependency have been described in the literature (Mutschler *et al.*, 2010). However, some recent preclinical studies and clinical trials have examined the potential of dextromethorphan to prevent tolerance and withdrawal from morphine (Jasinski, 2000; Manning *et al.*, 1996; Mao *et al.*, 1996), heroin (Vosburg *et al.*, 2011), or methadone (Cornish *et al.*, 2002). Ketamine and MK-801, but not ifenprodil, produce conditioned place preference (Suzuki *et al.*, 2000). Dextromethorphan, a NR1/NR2A-containing NMDA receptor –preferred antagonist, dose-dependently substituted for discriminative stimulus effect of ketamine that produces conditioned place preference (Table, Narita *et al.*, 2001).

8. Abuse potential

Dextromethorphan is readily available for purchase or theft in a number of over-the-counter cough and cold preparations (see above) and is referred to as dex, DXM, robo (Robo-tripping), skittles (skittling), poor man's PCP, red devils, tussin, vitamin D (Carr, 2006). A concentrated dextromethorphan powder can be extracted by various methods from cold preparations, e.g. Coricidin HBP Cough and Cold tablets (street name Triple C). In recent years, dextromethorphan has appeared in Ecstasy (MDMA) mimic or combination tablets (DEA, 2003).

Dextromethorphan abusers report a heightened sense of perceptual awareness, altered time perception, and visual hallucinations. Abusers of dextromethorphan describe the following four dose-dependent "plateaus":

Table 1: Plateaus of behavioral effects after dextromethorphan (Third-Plateau, 2008)

Plateau	Dose (mg)	Behavioral Effects
1 st	100–200	Mild stimulation
2 nd	200–400	Euphoria and hallucinations
3 rd	300–600	Distorted visual perceptions Loss of motor coordination
4 th	500–1500	Dissociative sedation
“Sigma”	1500–3000 (divided)	Same as 4 th except for a longer experience

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

Dextromethorphan is widely used as an antitussive in many over-the-counter and prescription-only preparations. It increases the threshold for cough at the level of the medulla oblongata (Mansky *et al.*, 1970). Its effectiveness in patients with pathological cough has been demonstrated in controlled studies: its potency being nearly equal to that of codeine. Compared with codeine, dextromethorphan produces fewer subjective and gastrointestinal side effects (Matthys *et al.*, 1983). At therapeutic dosages, the drug does not inhibit ciliary activity, and its antitussive effects persist for 5 to 6 hours. Its toxicity is low, but extremely high doses may produce central nervous system depression. However, recent randomized controlled trials suggest dextromethorphan has limited efficacy, if any, in children and adolescents (Schroeder *et al.*, 2004).

Other potential therapeutic uses for dextromethorphan are currently being investigated. Through its activity as a noncompetitive NMDA antagonist, dextromethorphan decreases glutamate activity. This attribute is suggestive of a potential neuroprotective role for such conditions as amyotrophic lateral sclerosis or methotrexate neurotoxicity (Drachtman *et al.*, 2002; Hollander *et al.*, 1994) or a reduction of pain sensation by reducing the excitatory transmission of the primary afferent pathways along the spinothalamic tract (Woolf *et al.*, 1993). Some clinical trials in postoperative cancer patients have demonstrated that dextromethorphan may reduce pain intensity, sedation, and analgesic requirements (Weinbroum, 2005; Weinbroum *et al.*, 2003). Dextromethorphan co-administered with quinidine, a specific inhibitor of CYP2D6 activity, has shown significant efficacy in treating the emotional disorder of pseudobulbar effect in both multiple sclerosis and amyotrophic lateral sclerosis (Miller *et al.*, 2007). However, dextromethorphan in combination with quinidine maintenance has a limited role in the treatment of opioid dependence (Vosburg *et al.*, 2011).

10. Listing on the WHO Model List of Essential Medicines

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

At the WHO Expert Committee on the Selection and Use of Essential Medicines from 31 March to 3 April 2003 the Committee concluded that there was insufficient evidence to support the listing of dextromethorphan (oral solution) as an essential medicine and recommended that the item be deleted.

11. Marketing authorizations (as a medicine)

Dextromethorphan is readily available for purchase in a number of over-the-counter cough and cold preparations (see annexe 1, report of the WHO questionnaire for the review of psychoactive substances for the 35th ECDD). Of the countries that responded to the questionnaire France was the first country to grant market admission in 1946. The most recent distributions on the market were done by Armenia and Moldova in 2004.

12. Industrial use

There is no industrial use reported in the literature.

13. Non-medical use, abuse and dependence

Cases of recreational abuse of dextromethorphan have been reported in United States, Sweden, Australia, Germany, and Korea (Chung *et al.*, 2004; Monte *et al.*, 2010; Murray *et al.*, 1993; Rammer *et al.*, 1988; Wolfe *et al.*, 1995) primarily among adolescents and young adults. The 2006 Monitoring the Future (MTF) Study showed that 4%, 5%, and 7% of 8th, 10th, and 12th grade students, respectively, reported nonmedical use of dextromethorphan during the previous year. This was the first year dextromethorphan was added to this survey for students (MTF, 2006). However, the misuse of OTC cough and cold medicines containing dextromethorphan for 8th graders, increased slightly 10th graders and dropped significantly for 12th graders in the MTF 2011 survey (MTF, 2011). Poison control centers reported that dextromethorphan abuse and misuse has rose from 99 in 1998 to 505 in 2009. The average age of subject in the abuse and misuse cases was 21 from 1998 to 2009 but the average age in 2009 was 17. This observation demonstrate the easy access minors have to dextromethorphan containing products. Another trend emerging is for older individuals (30-40 yr) to combine dextromethorphan with benzodiazepines.

However, these reports are still relatively infrequent (CEWG, 2009). A 6-year retrospective study from 1999 to 2004 of the California Poison Control System (CPCS) showed a 10-fold increase in the rate of dextromethorphan abuse cases in all ages and a 15-fold increase in the rate dextromethorphan abuse cases in adolescents (75% of the total 1382 cases). Based on SAMHSA's 2006 National Survey on Drug Use and Health, about 3.1 million persons aged 12 to 25 (5.3%) had ever used an over-the-counter cough and cold medication recreationally and 1 million persons aged 12 to 25 (1.7%) had used an over-the-counter cough and cold medication to get high in the past year. Young adults aged 18 to 25 were more likely than youths aged 12 to 17 to have used OTC cough and cold medications non-medically in their lifetime (6.5% vs. 3.7%) but were less likely to do so in the past year (1.6% vs. 1.9%). Whites aged 12 to 25 (2.1%) were more likely than Hispanics (1.4%) and blacks (0.6%) to have used an over-the-counter cough and cold medication in the past year to get high (NSDUH, 2006). A large scale analysis from the USA National Poison Data System data collected between 2000 and 2010 revealed a total of 44,206 dextromethorphan abuse cases, 34,755 of which were single-substance exposures. The mean annual prevalence of dextromethorphan cases reported to poison control centers was ~13 cases per million population for all ages and 113 cases per million for 15-19 year olds. The prevalence of dextromethorphan cases for all ages increased steadily until 2006 to a peak of 17.6 calls/million and the cases were predominantly male adolescents. The prevalence of abuse the following years hit a plateau at ~16 cases per million in 2010. It is likely that a combination of legislative, educational, and economic initiatives are responsible for the observed plateau (Wilson *et al.*, 2011).

The 2008 WHO questionnaire for the review of psychoactive substances for the 35th ECDD (annex 1) found that 9 countries of the 56 countries responding, reported on the use of dextromethorphan in a harmful way. Seven countries reported on the extent of harmful use.

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

Dextromethorphan is abused by individuals of all ages but its abuse by teenagers and young adults is of concern. This abuse is fueled by dextromethorphan's over the counter availability, legality, inexpensive price, and the extensive "how to" abuse information on various websites. The sale of the powdered form of dextromethorphan over the Internet poses additional risks due to the uncertainty of composition and dose. However, toxicity is rare and somewhat self-limiting and reports of dependence are infrequent. This suggests that simple steps to limiting availability through marketing and purchasing constraints would be sufficient to limit dextromethorphan misuse and abuse.

According to the 2008 WHO questionnaire for review of psychoactive substances for 35th ECDD (Annex 1), when abused, dextromethorphan is administered orally in large amounts and the experience varies by dose. Recreational doses can vary and range from 100 mg to 1200 mg or more. Low doses produce a mild stimulant effect. Moderate doses generally produce intoxicating effects that are sometimes compared to alcohol or cannabis use. In high doses dextromethorphan acts as a dissociative hallucinogenic substance and can cause a feeling of separation from one's body. Warnings regarding dangerous interactions with other substances (e. g. dextromethorphan + MDMA) are quoted. In the USA dextromethorphan is reportedly abused in combination with alcohol by adolescents primarily for its hallucinatory effects. It is abused by all age groups, however abuse in the adolescent population is especially a concern.

15. Licit production, consumption and international trade

Dextromethorphan is produced commercially in a number of countries including Belgium, Germany, France, Italy, Japan, Spain, Austria, Switzerland, and the United States. Dextromethorphan production is a complex and time-consuming process, making clandestine production impractical.

The 2008 WHO questionnaire for review of psychoactive substances for 35th ECDD (Annex 1) found that 26 countries import the substance. In 9 countries dextromethorphan is manufactured and also imported in the country. Bangladesh and China are the only countries that manufacture dextromethorphan and do not import the substance. Jamaica and Thailand import the raw material and manufacture it.

16. Illicit manufacture and traffic and related information

A concentrated dextromethorphan powder can be extracted by various methods from different cold medicines. In recent years, dextromethorphan has appeared in Ecstasy (MDMA) mimic or combination tablets (DEA, 2003).

Clandestine manufacturing and smuggling are not reported in the 2008 WHO questionnaire for review of psychoactive substances (annex 1).

17. Current international controls and their impact

No current international controls under any of the international drug control conventions.

18. Current and past national controls

According to the report of the WHO questionnaire in Annex 1 of the document, 12 countries reported that dextromethorphan is controlled under legislation that is intended to regulate availability of substances of abuse.

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

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Annex 1: WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD: Dextromethorphan

The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for dextromethorphan by 56 countries.

LEGITIMATE USE

48 countries authorized dextromethorphan as a medical or veterinary product. 5 countries legitimated dextromethorphan for technical use and one country, Syria, has authorized dextromethorphan for other legitimate use.

Of the countries that responded to the questionnaire France was the first country to grant market admission in 1946. The most recent distributions on the market were done by Armenia and Moldova in 2004.

In 17 countries the registered indication for dextromethorphan is antitussive. In 21 countries the registered indication is (nonproductive) cough (suppressant). In 4 countries, Brunei, the Czech Republic, Moldova and the United Arab Emirates, it is registered for a cold. In Israel for symptomatic relief of cough. In 2

countries it is registered for the flu, the Czech Republic and Lithuania. The Czech Republic indicated also, acute and chronic respiratory tract diseases, accompanied by non-productive irritant cough, fever, flu and cold symptoms relief, headache, muscle pain, non-productive irritant cough, symptomatic treatment of febrile viral infections, shivers, sore throat and stuffy nose. Germany indicated respiratory, cough and cold preparations, antitussives, exclusive combination with expectorants, opium alkaloids and derivatives. In Germany it has also found other uses in medicine, ranging from pain relief to psychological applications.

In Armenia, Burkina Faso, Costa Rica, and the Dominican Republic it is used off-label for antitussive. It is used as a syrup, tablets, liquid-filled gel capsule, paediatric drops, elixir, linctus (syrup), nasal drops, decongestants, antihistamine, suspension, chewable tablet, effervescent tablet, paediatric mixture, caplet and powder.

The dosage use varies between 10 mg/5 ml and 150 mg/150 ml for syrup. For tablets between 2,5 mg and 325 mg (1200 mg for recreational use), for capsules between 7.5 mg and 20 mg and for suspension between 6,7 mg/5 ml and 111 ml/100 mg.

26 countries indicated that they import the substance. In 9 countries dextromethorphan is manufactured and also imported in the country. Bangladesh and China are the only countries that manufacture dextromethorphan and do not import the substance. Jamaica and Thailand import the raw material and manufacture it.

ABUSE

Of the 56 countries responding, 9 countries reported on the use of dextromethorphan in a harmful way and 7 countries reported on the extent of the harmful use. When abused, dextromethorphan is administered orally in large amounts. In Germany the dextromethorphan abuse is for recreational use. The experience varies by dose. Different recreational dose ranges are sometimes described in terms of plateaus of effects. Low doses produce a mild stimulant effect. Moderate doses generally produce intoxicating effects that are sometimes compared to alcohol or cannabis use. In high doses dextromethorphan acts as a dissociative hallucinogenic drug and can cause a feeling of separation from one's body. The effects are sometimes compared to the effects of other dissociatives such as PCP or ketamine. The dosages of dextromethorphan vary greatly, depending on the individual and the desired level of effects. Recreational doses range from 100 mg to 1200 mg or more. Warnings regarding dangerous interactions with other substances (e. g. dextromethorphan + MDMA) are quoted. In the USA dextromethorphan is reportedly abused in combination with alcohol by adolescents primarily for its hallucinatory effects. It is abused by all age groups, however abuse in the adolescent population is especially a concern. In the Czech Republic the extent of the harmful use is approximately 3% of the party goers, last year and last month approximately 2%. In Denmark there are no systematic reports about the scope of abuse. However, there are sporadic reports about abuse in youth settings. Germany reported not having detailed data on the extent of harmful use available. In the USA the MTF survey showed that in 2007, 4.0% of 8th graders (vs. 4.2% in 2006), 5.4% of 10th graders (vs. 5.3% in 2006), and 5.8% of 12th graders (vs. 6.9% in 2006) reported abuse of over-the-counter cough or cold medication.

5 countries reported on the extent of public health or social problems associated with the harmful use of dextromethorphan, while 3 countries reported not having information or data related to public health or social problems associated with the harmful use of dextromethorphan. The Czech Republic reported not having any case of overdose caused by dextromethorphan. In Denmark dextromethorphan was a contributing case to 6 deaths between 2001 and 2006. In one case only, the dextromethorphan concentration found could have caused a deathly poisoning. All 6 deaths involved combination poisonings, as other substances, besides dextromethorphan, were found in doses that could cause a deathly poisoning. In the period medio August 2006 and primo April 2008 there had been 26 inquiries about dextromethorphan in connection with poisonings. In 11 of these incidents dextromethorphan was used by young people of compulsory school age. None of these incidents were fatal. No information on dextromethorphan dependence is available. The Republic of Korea reported that if it is overdosed, hallucination, mental disorder, dyspnea, state of coma and death may occur. In the USA medicines containing dextromethorphan were involved in an estimated 10,117 emergency department (ED) visits involving the nonmedical use of pharmaceuticals in

2006. This represents a 70% increase from 2004, when dextromethorphan was involved in 5,962 nonmedical uses ED visits. In 2004 there were an estimated 16,858 ED visits involving a dextromethorphan product, and of those, 5,962 (35 %) were associated with non-medical use of pharmaceuticals. About half (51%) of the dextromethorphan nonmedical use ED visits involved patients aged 12-20. Alcohol was involved in about 13% of ED visits involving nonmedical use of dextromethorphan for patients aged 12-17, 41% of ED visits for patients aged 18-20, and 61% of ED visits for patients aged 35-54. Suicide attempts involving dextromethorphan accounted for 17% of dextromethorphan-related ED visits.

CONTROL

12 countries reported that dextromethorphan is controlled under legislation that is intended to regulate availability of substances of abuse. In Germany dextromethorphan is not subject of drug control regulations. However in cases of illegal production, circulation, trading or passing of dextromethorphan a violation of the Pharmaceuticals Act may be considered.

In total 2 countries have tracked illicit activities involving the substance. Clandestine manufacturing and smuggling are not reported. Diversion is reported once and other illicit activities are reported also one time.

2 countries reported on the quantity of the seizures. Malaysia reported seizures of 1.2kg, 4000 of 30mg tabs and the USA reported 7 seizures (0.21g of powder, 157.6 tabs) in 2007.

IMPACT OF SCHEDULING

16 countries reported that if dextromethorphan is placed under more strict international control, the availability for medical use will be affected. 12 countries reported how a transfer will impact the medical availability. Armenia indicated that the process of prescribing and getting them from the appropriate place will be difficult. According to Australia it may likely result in a price premium for these medications and may lead to lessened availability or convenience as a common cough suppressant. China reported that the availability will be decreased. Cyprus, reported that a restriction will only deprive patients from a useful cough suppressant. Japan imagined that strengthening control would be severely influential amongst consumer, stakeholder and so on. Lithuania reported also that the availability of these products will be negatively affected because at present these are available without prescription. Myanmar indicated that the medical availability will become limited in remote areas of the country and in places where authorized professionals are not available. The assumption in the Netherlands is that physicians are reluctant to prescribe a drug of abuse for a minor indication. According to the Republic of Korea the administrative process in distribution will be a little bit more complicated. Thailand reported that the drug may be more expensive since the price of raw material would rise due to more strict control on raw material import and export increasing cost of administration for manufacturers. Strict measurement on drug distribution would make it more difficult to access for the general public. Tuvalu reported also that it will affect the availability. Finally the USA reported that dextromethorphan-containing drug products would not be easily accessible to the patient because patients would be unable to purchase the products without a prescription from a health care provider. Increased utilization of the health care system by patients to obtain a prescription for these products would likely increase healthcare costs.

Dextromethorphan (pINN)

Actifed Dm, Aurimel, Acatar, Actifed new, Alicol, Ambroxol, Dextrometorfano, Ambroxol, Agrip, Actifed, Asafen Forte, Actifed Toux seche, Activox toux seche, Almatussil, Adultes, Atuxane, Acamol Tsinun & shapa'at day, Acamol tsinun & shapa'at night, Alcinal, Adol,

Avophan, Axcel dextromethorphan, Antalgese, Akindex, Aquitos, Actifed-dm, Alphacold, Almafen D-M, Act-3 CTD, Antus, Antus 1, Antussan, Asadex, A-Tussin, Actiolem, Adol cold, Alka-Seltzer Plus, Allfen, Ambifed, Amerituss, Anaplex, Andehist.

Brofex, Benafed, Benadryl, Bisolvon, Balsoclast dextromethorphan, Benylin, Bronchosedal, Beathorphan, Balsedrina, Bick 44, Bye-Flu, Broxial, Broncoler, Bromhydrate de dextromethorphan bouchara recordati, Bronchotonine toux seche, Broncorinol toux seche, Buckley's, Buckley's DM, Broncholar foree, Broncholar, Bronchophane, Biscokol, Benadryl, Bisoltussin, Bexatus Bicasan, Brodex, Brodimexine, Benidex plus, Benacof, Benical, Benical cold, Bronkar-A, Bronchophane, Broncholar, Broncholar forte, Benadryl DM, Bromadine, Bromfed.

Cepacol, Chericof, Colfed, Contrasal, Comtrex, Contrex forte, Coldrex, Chemitusin, Caltilin-1, Catocil, Candibron, Capsyl, Codotussyl toux seche, Corcidin, Chile dough, Coldex D, Colfed DM, Coflex, Cinfotos, Cinfatos, Couldetos, Capa, Celo, Cetussin, Commiccap, Commicmet, Co-Off, Cortuss, Coldex-D, Cardec, Cheracol, Codal, Codimal, Comtrex, Contac, Coricidin, Cough-X, Cydec.

Dextrokuf, Dextrolag, Dextrose, Demazin, Dimetapp, D-cough, Dephan, Dexdol, Dexophan, Dextrophan, Dextrin, Dextroforme, Dimetapp, Dhasedyl, Day Nurse, Dexcophan, Dynaphan, Diacol, Daleron, Dr. Rentschler Hustenstill, Dretox, Dextrocidine, Dextussil, Drill, Destro Bolder, Dextrocap, Dextromethorphan, Dexamolcold, Daleron Cold 3, Dexofen, Dextrophen, Dexcophan, Dextrokuf, Dec, Decal, Decof, Depan – F, Dex - Co – Tab, Dex, Dexceryl, Dex-Cough, Dex-Cough-Mp, Dexen, Dexfan, Dexphan, Dexto, Dextolar, Dextra, Dextramet, Dextresan, Dextro, Dextrobromide, Dextro-Brywood, Dextrodon, Dextrodon-S, Dex-Trodon-T, Dextrolyl Cough, Dextromed, Dextropac, Dextrophen, Dextroral, Dextrosia –15, Dextrosin, Ditromet, Defeks, Deksan, Dorfan, Dorfan CF, Dextrokuf, Dextrolag, Diabetic choice, Diabetic Tussin, Dimetapp, Donatussin, Duratuss.

Exedexe, Expectoflug, Ergix, Exedexe, Efidex-D, Eblatuss, Eifcof, Eifcof – B, Eifcof – G, Etetal, Exedexe, Emikoff.

Fludisoft, Flumed Dm, Fluditec, Fludil, Fluditos, Fludibron, Fusalar, Fluditec, Federtussin DM, Formulatus, Frenatus, Flu out-d, Fluout fort C, Flu out fort N-D, Fulamine, Flumed DM, Fenesin.

Gutibenna plus, Gripamil, Gripex, Grippe-stop, Grippe stop ctd, Gani-tuss, Guaifenesin DM, Guaifenex, Guiatuss.

Humex, Histatussin DM, Hatso, Hayaspect, Humibid.

Ipesandrine, Iniston, Icolid, Iyafin De15.

Kafosed, Kintuxil, Kafi-Kuf, Kimipect, Kanadol-flu, Kidkare.

Lavitussin, Lasoltussin, Lastuss, Lohak.

Mentex, Mucotussin, Mucotussin, Mucorex, Medofed, Mucobron, Methor, Mesocon, Mini, Mano-Dextro, Manodextro, Mano-Drex, Methorphan, MIm – Dex, Metorfan, Mentex, Maxifed, Mucofen.

Nortussine, Nortussine, Noscaphan, Nospan, Neumonil, Notussan, Nodex, Nortussine, NeuTussan, Nocuf, Night Nurse, Numark, Nirolex, Norco, Norcof, Norcough, Neocoff-DM.

Occitux, Quintopan.

Pectolyn, Panadol multisymptom, Phenetaps DM, Paralen Plus, Pulmotos, Petocalm, Privatux, Pulmodexane, Paramol AF & Shiul day care, Paramol AF & Shiul night care, Pharmaniaga, Pusiran. Parlatos, Pulmosanyl, Polycough, Polydex, Polydex P, Polydex Y, Premodex, Protussa, Paranorm, PediaCare, Phenergan, Profen, Prometh, Protuss.

Robitussin, Rhinotussal, Riaphan, Robitussin Dm, Romilar, Rhinathiol, Romilor, Rinol, Robitussin DM, Rondex DM, Rfcindal, Rhinathiol, Robitussin sough DM, Robittusin DM, Rextromethorphan, Rumilar, Roxan-Tuss, Reemo-pect, Rondmax oral D, Rondi, Rhinotuss, Retrussan, Roexphan, Rotuss, Radyocodin, Rhinotussal, Romilar, Riaphan, Romin, Robitussin CF, Rescon, Robitussin Night Relief, Rondec.

Sedofan, Sedex, Saft, Sanitos, Sebrane, Strepsils toux seche, Silomat DMP, Sedamol, Sensamol cold night, Sunthorphan, Setustop, Serratos, Streptuss, Sedafen, Softime, Sedata, Santass, Strepsils Dry Cough, St.Joseph, Sedofan DM, SINUtuss, Sudafed, Su-Tuss, Sfidex..

Tussinol, Tripofed Dm, Tripofed expectorant, Tussivan-N, Tussidex, Toux-san, Toxium, Tussipect, Tusso, Tussils, Tabcin, Theraflu, Toscal, Tusilexil, Tussis, Tylenol cold, Tylex flu, Tussidrill, Tylex, Triaminic RT, Teraflu, Tussin OM, Toflus, Tusitos, Tusidol, Tussidane, Tuxium, Tussibay, Tussicure, Tussilar, Tarodex, Theraflu cough & colds, Tiptipot Kofli, Tussin DM, Tussophedrine NF, Triaminic, Tussinore, Tussidex Forte, Tussin, Tussin-forte, Tussilen, Tusorama, Terasil-D, Tussidrill, New tussi-grip, Tussi-grip, Tussiphan, Tullin, Tullin-D, Toxil, Tussi-free, Tussl, T.Man Cough (D.M.), Throatil Dex, Tromet, Tromet, Tusadon, Tusco, Tussanyl, Tussils, Tussipax, Triatus, Tucodil, Tylo col, Tussis OM, Safe Tussin, Theraflu, Touro, Triaminic, Tussafed, Tuss-DM, Tussex, Tussi-Organidin, Tylenol cold, Hydro-Tussin.

Unifed DM.

Vicks vaposyrup, Vicks, Virusfree, Vaposyrup.

Winco, Windex, Wintus.

Zopcof, Zopcof Syrup, Zopcof-A Syrup.

Form

- Oral
- Syrup
- Tablet
- Liquid-filled gel capsule
- Paediatric drops
- Elixir
- Nasal drops
- Suspension
- Chewable tablet
- Effervescent tablet

- Paediatric mixture
- Caplet
- Powder

Other legitimate use

Use in medicines, ranging from pain relief to psychological applications.

Off-label

- Antitussive
- Therapeutics
- Cold and cough medicines