Critical Review Report:
Diphenidine

Expert Committee on Drug Dependence
Forty-third Meeting
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This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.
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References
Executive summary

This critical review has been proposed based on information brought to WHO’s attention that the legal status of diphenidine is currently a grey area. This drug is easily obtainable from online shops and it is manufactured by several chemical companies. Case reports have noted that the ingestion of this new psychoactive compound can lead to severe intoxication and death.

Diphenidine is a dissociative substance of the 1,2-diarylethylamine class. The first report of its synthesis was in 1924, but its recreational human use was not reported until 2014. Since the history of human usage of diphenidine is so short (approximately 7 years), little is known about its pharmacological properties, metabolism and toxicity.

Diphenidine is an N-methyl-D-aspartate (NMDA) receptor antagonist with affinity to the binding site similar to ketamine. The two enantiomers of diphenidine differ in their ability to block the NMDA receptor: the (S)-enantiomer has a 40 times higher affinity for the receptor than the (R)-enantiomer. Diphenidine is structurally related to 2-MEO-diphenidine (2-MXP).

Diphenidine has dissociative ketamine-like effects at doses starting at around 50–100 mg when administered by the oral and parenteral routes. Subjective effects include depersonalization and disconnection effects. It can induce euphoria, but users of diphenidine also describe it as an unpleasant experience. Diphenidine can induce a hallucinogenic state known as “dissociative anaesthesia”, which can lead to a feeling of being detached from the body. The duration of action is apparently 2–8 hours based on reports from online forums and published case reports.

Recent case reports have described the detection of diphenidine and have noted an association with acute ketamine/phenycyclidine (PCP)-type toxicity and deaths. Published information on four fatal cases associated with diphenidine mostly involved multiple substances. Scientific publications on diphenidine mostly date from 2014 to 2018. The lack of recent publications about diphenidine may suggest that there has been less scientific interest (and most likely no recent fatal cases) in the past two years.

Diphenidine has been studied and patented as one of a group of 1,2-diarylethylamines considered to have potential as a treatment for neurotoxic injuries. However, there is no experimental evidence for these potential therapeutic applications although some anecdotal user experiences indicate antidepressant effects.

In summary, diphenidine is not approved for any medical or veterinary use. It is used for recreational purposes mainly in Europe, Japan and the United States of America. It is available through the Internet in powder form for oral administration, smoking or vaporization, or nasal application. Since it first appeared on the drug market in 2013, seizures have been reported from around the world and its use has resulted in several cases of severe intoxication and death, which have led to its scheduling in Canada, Germany and the United Kingdom.
1. Substance identification
   A. International Nonproprietary Name (INN)
      NA
   B. Chemical Abstract Service (CAS) Registry Number
      36794-52-2
   C. Other chemical names
      diphenidine, DPD, 1-(1,2-diphenylethyl)piperidine, 1,2-DEP
   D. Trade names
      NA
   E. Street names
      Although it has no common street names, diphenidine was sold in Japan in 2014 as a herbal mixture with white powder under the name “ALADDIN SPACIAL EDITION”. This seized material had a high content of diphenidine in the presence of 5-fluoro-AB-PINACA (1).
   F. Physical appearance
      Powder, tablets
   G. WHO review history
      Diphenidine has not previously been pre-reviewed or critically reviewed by the WHO Expert Committee on Drug Dependence.

2. Chemistry
   A. Chemical name
      IUPAC name: (±)-1-(1,2-diphenylethyl)piperidine
      CA Index name: NA
   B. Chemical structure
      Free base:
      Molecular formula: C_{19}H_{23}N
      Molecular weight: 265.4 g/mol
Fig. 1

Structure of diphenidine

Source: PubChem.

C. Stereoisomers

Diphenidine is chiral. Two studies reported large differences in $N$-methyl-$d$-aspartate (NMDA) receptor affinity between the two enantiomers of diphenidine: (+)-(S)-diphenidine showed a 40-times higher affinity than the (−)-(R-) enantiomer (2, 3). These pronounced differences make the development of chiral separation methods necessary.

D. Methods and ease of illicit manufacturing

Diphenidine was first synthesized in 1924 by Christiaen (4) who used a modified Bruylants reaction.

Since then, other publications have described the preparation of diphenidine and various analytical characterizations. For example Wallach et al. published a detailed description of the synthesis of diphenidine (5). The starting material is 1,2-diphenylethanamine, which is a precursor for synthesis of (+)-(S)-1-(1,2-diphenylethyl)piperidine. The two separated enantiomers of 1,2-diphenylethylamine can also be used as precursors for synthesis of the isomers (S)- and (R)-1-(1,2-diphenylethyl)piperidine (3), which allows the production of high-potency (+)-(S)-diphenidine.

In general, diphenidine can be synthesized within a few days from commercially available 1,2-diphenylethanamine followed by reaction with the corresponding dibromoalkane (Fig. 2) (5). All reagents and high-performance liquid chromatography (HPLC)-grade solvents can be obtained without restrictions from chemical companies.
E. Chemical properties

Melting point 210 °C

Boiling point 351.3 ± 11.0 °C at 760 mmHg

Solubility Diphenidine is soluble in organic solvents such as ethanol (30 mg/mL), dimethyl sulfoxide (DMSO) (30 mg/mL), and dimethyl formamide (50 mg/mL). An organic solvent-free aqueous solution of diphenidine HCl can be prepared by directly dissolving the crystalline solid in aqueous buffers (for example, in phosphate-buffered saline at pH 7) (7).

F. Identification and analysis

The available methods for the determination of diphenidine in biological materials were summarized by Katselou et al. (6). The first of these methods was described by Kudo et al. (8) who used liquid chromatography-mass spectrometry (LC–MS-MS) for the determination of diphenidine in blood and urine samples. They reported a limit of detection of 1 ng/mL. This method was verified in postmortem biological fluids (8). At the same time, diphenidine was detected for the first time in Europe in seized materials that were analysed by gas chromatography- mass spectrometry (GC-MS) in forensic laboratory in Italy in from 2013 to 2015 (9). GC-MS can be used both as a general screening method and for the quantification of diphenidine and related compounds in seized bulk material (10). A similar method to the one described by Kudo et al. (8) was used by Hasegawa et al. (11) to detect and quantify diphenidine in blood, urine and seized bulk material.

Minakata et al. (12) published a description of a Matrix-assisted laser desorption/ionization-quadrupole time of flight–mass spectrometry (MALDI-QTOF/MS) method for the determination of diphenidine and its metabolites in blood and urine. The quantification range was 3–100 ng/mL. This method was verified in postmortem samples of blood and urine (12).

The coexistence of diphenidine with the synthetic cannabinoid 5-fluoro-AB-PINACA was identified in a herbal product in Japan by both GC-MS and electrospray ionization-tandem mass spectrometry (ESI-MS). The content of diphenidine in the herbal product was as high as 289 ± 23.2 mg/g which exceeds even very high doses of this drug, especially when it is smoked or vaporized (1). High-resolution ESI-MS can also be used to differentiate the enantiomers of diphenidine (5).

Salomone et al. (13) reported on a new ultra-high-pressure-LC–MS-MS method to detect diphenidine in hair samples. They used this method to re-examine 54 hair samples, which had previously tested negative during regular drug screening. Six of the samples tested positive for diphenidine. Using a similar approach, diphenidine has also been detected in a hair sample 49 days after a single administration of diphenidine (14).
3. Ease of convertibility into controlled substances

Diphenidine is not readily converted into other internationally controlled substances.

4. General pharmacology

A. Routes of administration and dosage

Diphenidine is psychoactive when administered via the oral and parenteral routes (15). According to reports on user forums active oral doses start at around 50–100 mg; doses of more than 150 mg are described as strong. The duration of action has been reported as 3–6 hours and 2–5 hours based on user reports in online forums (16, 17). The onset of effects occurs 15–30 minutes after oral ingestion. The duration of after-effects ranges from 4 to 24 hours – the after-effects are also known as a “hangover” or an “afterglow”.

Diphenidine is reported to have a much more rapid onset of effects and a shorter half-life when vaporized or smoked. Vaporization apparently requires as little as 20% of a standard oral dose to produce the same effect (18). Common doses used for smoking are between 20 and 40 mg, whereas strong doses range from 40 to 55 mg, and heavy ones are greater than 55 mg. The onset of effects after inhalation occurs within 30–90 seconds, with a peak effect between 0.5 and 2 hours, and an after-effect duration of 2–5 hours.

B. Pharmacokinetics

A summary of the pharmacokinetics of diphenidine has been published by Wallach & Brandt (15). In short, diphenidine is a tertiary amine and a weak base, which explains its highly lipophilic properties and high concentrations of diphenidine have been detected in fat tissue of postmortem samples. This is supported by the findings of Hasegawa et al. (11) who reported on a fatal case involving diphenidine and the synthetic cannabinoid receptor agonists 5-F-AMB and AB-CHMINACA. They were able to detect diphenidine in several solid tissues and found the highest concentration in adipose tissue (11).

Wink et al. (19) studied the phase I and II metabolism of diphenidine in rat and human liver microsomes. Diphenidine was administered at a dose of 20 mg/kg body weight to identify the metabolites, and one 1 mg/kg dose (by gastric intubation), which corresponds roughly to users’ doses. The rats were housed in metabolism cages for 24 hours and urine samples were collected. Diphenidine was found to be extensively metabolized via various pathways. Based on the metabolites identified in rat urine, the authors proposed the following metabolic pathways (19): “mono- and bis-hydroxylation followed by methylation of one of the hydroxy groups, N,N-bis-dealkylation, and combinations of them as well as glucuronidation”. A metabolic screen in human liver microsomes was conducted to find out whether the metabolites detected in rat urine are also formed in humans. The mono- and bis-hydroxy as well as the oxo- metabolites were also detected in this preparation (19). Finally, the authors also studied the involvement
of the CYP isoenzymes. CYP1A2, CYP2B6, CYP2C9 and CYP3A4 were all found to be capable of forming the initial metabolites (19).

Two major metabolites identified in the metabolic screen by Wink et al. (19) were also detected in blood and urine samples from a fatal case involving diphenidine. These metabolites resulted from mono-hydroxylation of the piperidine ring and mono-hydroxylation of the phenyl ring (12). In another fatal case involving diphenidine and the synthetic cannabinoid receptor agonist 5F-ADB, five different mono- and dihydroxy metabolites of diphenidine were detected in blood and urine, and metabolic pathway analysis for diphenidine indicated that hydroxylation on any of the ring moieties is possible (20).

C. Pharmacodynamics

Effects in vitro

Diphenidine is an NMDA receptor antagonist. Electrophysiological studies suggest that diphenidine provides receptor antagonism via an uncompetitive channel-blocking effect (21). However, diphenidine induces its specific subjective and mind-altering effects not only by NMDA receptor inhibition, but also by inhibition of monoamine neurotransmitter transporter activity (especially of the dopamine transporter (DAT)); interactions with opioid and sigma receptors and active metabolites may also contribute to the effects of diphenidine (16, 22).

Diphenidine blocks NMDA receptor-mediated field excitatory postsynaptic potentials (fEPSPs) in rat hippocampal slices (21). This is consistent with the effects of a channel blocker such as MK-801 – which is the gold standard for uncompetitive NMDA receptor blockade. As well as diphenidine, several related compounds and known NMDA receptor antagonists were recently studied to determine their effects on NMDA receptor-mediated fEPSPs. The rank order of potency for inhibition was found to be MK-801 > PCP > diphenidine > 3-MXP > 2-MXP > ketamine > memantine (21). This order closely paralleled NMDA receptor affinities (15, 21).

Two studies reported the inhibitory constant (Ki) value at the NMDA receptor for diphenidine: Ki = 18 nM (21) and Ki = 39 nM (2), respectively.

As monoamine reuptake inhibition is up to two orders of magnitude lower in potency relative to the NMDA receptor, the contribution of dopamine, serotonin and norepinephrine to the drug effects of diphenidine is suggested to be of less relevance. However, a contribution, particularly of the DAT Ki = 317 nM (21) and Ki = 230 (23) to the potential abuse liability of this drug, especially in cases of high doses or overdoses, cannot be excluded.

Importantly, although little discussed in the literature, diphenidine shows affinity for sigma receptors (σ1, Ki = 290 nM and σ2, Ki = 193 nM (21)). Although the functional interaction of diphenidine with the sigma binding sites is not known it is noteworthy that the σ1 receptor is a membrane protein expressed throughout the human body, which acts like an inter-organelle-signalling regulator and fine tunes electrical activity and calcium homeostasis.
Effects in vivo

Similar to classical NMDA receptor antagonists such as MK-801, a high dose of diphenidine (20 mg/kg) administered subcutaneously, significantly disrupted prepulse inhibition (PPI) of the startle reflex in rats (15, 21). PPI of the startle reflex is an established measure of sensorimotor gating. In particular, NMDA receptors in the hippocampus play a critical role in the regulation of PPI. PPI disruption caused by NMDA receptor antagonists may reflect alterations in information processing that contribute to their dissociative effects (25). However, diphenidine was less potent than ketamine in these PPI experiments (26), which was unexpected based on its higher NMDA receptor affinity (21). This suggests that pharmacokinetic effects and/or active metabolites might influence the potency of diphenidine in vivo. The reduced potency in PPI is consistent with reports of the drug’s relatively low potency in humans; common doses of diphenidine are around 50–100 mg.

Other behavioural effects of diphenidine were noted by Wallach & Brandt (15). Stereotypy was induced in rats following administration by three different routes. A median effective dose (ED$_{50}$) of 220 nmol (versus PCP 50 nmol) was calculated after intracerebroventricular infusions of diphenidine; after subcutaneous administration the ED$_{50}$ was 2.9 mg/kg and after intraperitoneal injection the ED$_{50}$ was 2.0 mg/kg (2). The (+)-(S)enantiomer of diphenidine was more potent in eliciting stereotypic behaviour (intracerebroventricular, ED$_{50}$ = 120 nmol/rat; subcutaneous, ED$_{50}$ = 0.78 mg/kg; intraperitoneal ED$_{50}$ = 2.1 mg/kg), which is consistent with a slightly higher NMDA receptor affinity compared to the racemate (2).

5. Toxicology

No data are available concerning the toxicity, reproductive impact and carcinogenic/mutagenic potential of diphenidine. The only available dataset concerns a median lethal dose (LD$_{50}$) estimation in mice that reported an LD$_{50}$ of 325 mg/kg after subcutaneous administration (27).

6. Adverse reactions in humans

Information from published case reports, the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) Tox-Portal and various Internet sources (listed in Annex 2) was reviewed. It shows that diphenidine can cause acute behavioural, emotional, motivational, cognitive and somatosensory and motoric changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, acute intoxication can lead to emergency department admissions or even death. Experiences described by 14 people who had taken diphenidine from 2014 to 2018 were retrieved from Erowid (28) and an additional 5 reports of user experiences were retrieved from Psychonautwiki (18).

Experiences reported by drug users show that the effect of diphenidine varies greatly from person to person and also with the dose taken (doses usually range from 50 mg to more than 150 mg). Effects following oral use occur after approximately 15–30 minutes. However, when smoked, there is a rapid onset of effects within seconds. The effect is also heavily dependent on the set and setting,
which is a common drug-use phenomenon. At higher doses (from 150 mg orally), hallucinations and out-of-body experiences can occur. Acute effects of diphenidine often include stimulation and, at high doses, sedation and amnesia. At lower doses, the intoxication is sometimes compared to the effects of ethanol. At higher doses perceptual alterations in all sensory modalities may occur. Hallucinations are particularly common. Cognitive effects include depersonalization, derealization and loss of ego boundaries as well as altered thought patterns, delusions and paranoia (15, 16). Overall, and especially at higher doses, diphenidine has ketamine-like effects – this finding is supported by their similar pharmacological properties. Several reports from diphenidine users have described it as an unpleasant experience.

Four diphenidine-related deaths (all with multidrug toxicity) and heavy intoxications have been reported in Europe and Japan. Fourteen nonfatal cases of diphenidine-related intoxication were recorded in Sweden in 2014 (29). Toxicological analyses confirmed the presence of diphenidine in blood (2–262 ng/mL) and urine (8–19 000 ng/mL). In 12 of the 14 cases other new psychoactive substances and classical drugs of abuse were also detected in the blood and urine samples. The following clinical signs were reported: hypertension, tachycardia, anxiety, and altered mental status including confusion, disorientation, dissociation and/or hallucinations. Nystagmus, meiosis and muscle rigidity were also seen (29). The patients recovered within 1–3 days after hospitalization. Three patients had plastic bags containing a white powder labelled “diphenidine”. The analysis of the powder using LC–MS-MS and nuclear magnetic resonance spectroscopy confirmed the presence of diphenidine, but no other psychoactive substances were detectable (29).

Gerace et al. (30) published a case report describing a 30-year-old man with a previous history of drug addiction who was found in a confused and agitated state and unable to communicate. Next to him was a small plastic bag labelled “Diphenidine 1 g”. The content of the bag was analytically confirmed by GS/MS. He had tachycardia, was agitated and disoriented with miotic non-reactive pupils. He was admitted to the emergency room and sedated with midazolam, diazepam and haloperidol. The patient regained consciousness within 90 minutes, but was still drowsy with slurred speech. He had no amnesia. Diphenidine concentrations measured in his plasma and urine were 308 and 631 ng/mL, respectively (methylphenidate and diclazepam were also found in his plasma) (30)). Diphenidine (4400 pg/mg) was also detected in a hair sample. The patient was discharged from hospital after 5 days.

A fatal intoxication of a 53-year-old male who had taken the synthetic cannabinoid receptor agonist 5F-ADB and diphenidine was reported by Kusano et al. in 2017 (20). Toxicological analysis revealed a blood concentration of 12 ng/mL diphenidine and 0.19 ng/mL 5F-ADB (20).

Hasegawa et al. (11) reported on a fatal case of a 30-year-old male who had taken diphenidine. Analysis of various tissues, blood and urine revealed the presence of AB-CHMINACA, 5F-AMB and diphenidine. A particularly high diphenidine concentration of 11 100 ng/g was measured in the adipose tissue (11).
Another fatal case was reported in Japan. A woman in her thirties was found dead on a bed. Considerable amounts of “aroma liquid” and “bath salt” products and hypnotic drug tablets were scattered beside the bed. Autopsy showed pulmonary congestion and oedema. Blood samples were positive for diphenidine (1380 ng/mL), three synthetic cathinones, ethanol and therapeutic concentrations of benzodiazepines (8).

Another autopsy case from Japan involved benzodiazepines and diphenidine. Quantitative toxicological analysis showed concentrations of diphenidine in femoral blood of 0.073 µg/mL. Death was attributed to combined toxicity due to multiple drug interactions. Congestion and oedema were reported (31).

The French Addictovigilance Network retrospectively analysed possible cases of diphenidine use from 2012 to 2016 and identified 11 cases. However, none of these cases was considered proven – these possible cases included psychiatric, neurological and cardiovascular problems (32).

7. Dependence potential
   A. Animal studies
      There are no reports on physical withdrawal reactions or development of tolerance in animals.
   B. Human studies
      Given its ketamine-like pharmacology it has been suggested that physical dependence is possible, and that withdrawal symptomatology may occur when a person stops using diphenidine. However, this assumption is so far not supported by any systematic study or by anecdotal case reports. Prolonged and repeated use of diphenidine may lead to tolerance. Cross-tolerance to other dissociatives may also occur (6). However, no published reports or user reports are available to support these general assumptions on dependence liability and development of tolerance.

8. Abuse potential
   A. Animal studies
      Sahai et al. (33) analysed the mechanism of binding and functional relevance between rat DAT (rDAT) and diphenidine, and the three structural MXP isomers using in silico and in vitro approaches. Besides docking simulations, molecular dynamics simulations in rDAT complexes (rDAT-diphenidine, rDAT-2-MXP, rDAT-3-MXP and rDAT-4-MXP) were conducted in biophysically relevant membrane environments. When diphenidine was bound to DAT, it led to a disruption of the extracellular network with the ionic interaction (a feature not seen with the other compounds). This suggests a mechanism involving a conformational change of the transporter molecule whereby DAT opens extracellularly (33). These in silico data are in line with the in vitro data published by Sahai et al. (33). Thus, diphenidine displaced RTI-121 binding (specific radioligand for the DAT) – in a comparable manner to that of cocaine (Fig. 3A). Diphenidine also evoked dopamine efflux in
the nucleus accumbens as measured by in vitro voltammetry; however, this effect was not as pronounced as with cocaine (Fig. 3B). In conclusion, this set of experiments does indicate that diphenidine exhibits pro-dopaminergic stimulant-type effects and from this neurochemical perspective there is an indication that this drug has abuse liability.

B. Human studies

No case reports or reports of any systematic study on abuse liability of diphenidine have been published.

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

Diphenidine is not approved for medical or veterinary use, and it has no industrial or other use (6). It is manufactured by several chemical companies (mainly for research purposes) and is also available from other sources. The medical use of diphenidine has not been explored; however, the class of 1,2-diarylethylamines (which includes diphenidine) may have clinical relevance in a range of therapeutic areas including management of pain, epilepsy, neurodegenerative disease, alcohol dependence and depression (6, 15).

An EU patent was approved (EP0346791 (B1)) for the chemical class of 1,2-diarylethylamines – which also includes diphenidine – for their potential use in the treatment of neurotoxic injury. In this patent, compounds, compositions and methods of treatment are described to control brain damage associated with anoxia or ischaemia, which typically follows stroke, cardiac arrest or perinatal asphyxia. The administration of a 1,2-diarylethylamine compound such as diphenidine inhibits excitotoxic actions, especially via NMDA receptor blockade.

The therapeutic potential of diphenidine may be provided not only by NMDA receptor blockade but also by its interaction with the σ1 receptor. Ligands targeting the σ1 receptor are being tested in clinical trials for treatment of Alzheimer’s disease, ischaemic stroke and neuropathic pain (24). The σ1 receptor activity of diphenidine may therefore contribute to its therapeutic potential. However, there is so far no experimental evidence or anecdotal report that would support such an assumption.

10. Listing on the WHO Model List of Essential Medicines

Diphenidine is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing authorizations (as a medicinal product)

Diphenidine has never been marketed as a medicinal product.

12. Industrial use

Diphenidine has no industrial use.
13. **Nonmedical use, abuse and dependence**

See section 6. Adverse reactions.

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

As described in section 6, a small number of cases of heavy intoxications with diphenidine that required hospitalization have been reported. In most of those cases, underlying psychiatric disorders and somatic diseases, and use of other drugs may have contributed to clinical complications. Impairment of memory function may persist for several days.

An estimation of public health problems is provided by the STRIDA project from Sweden. Over a 12-month period from January to December 2014, 750 cases of suspected drug intoxications originating from emergency rooms were studied. Fourteen of the patients were positive for diphenidine (diphenidine concentration in serum ranged between 2 and 262 ng/mL), which equals 1.9% of the high-risk population (30). The patients who tested positive for diphenidine required hospitalization for 1–3 days. In addition to standard supportive therapy, half of these patients were treated with benzodiazepines and/or propofol. The authors concluded that the adverse effects noted in patients with analytically confirmed intoxication involving diphenidine were similar to those reported for other dissociative substances such as ketamine and methoxetamine. However, the high proportion of polysubstance use might have played a role in the intoxication and clinical features (30).

No relevant publication or case report has appeared in the scientific literature in the past two years and there are no recent discussions of this drug on online forums. This lack of recent reports of severe intoxications, fatalities or user experiences, suggests a decreasing interest of the worldwide drug scene in diphenidine.

15. **Licit production, consumption and international trade**

NA

Please see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. **Illicit manufacture and traffic and related information**

NA

Please see Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. **Current international controls and their impact**

Diphenidine is not controlled under the 1961, 1971 or 1988 United Nations Conventions.
18. Current and past national controls

Legal status of diphenidine (summarized from references 6 and 18):

- Brazil: diphenidine has recently been included in Brazil’s controlled substances lists because of its potential to cause harm to public health.
- Canada: diphenidine has been a schedule I controlled substance since March 2016.
- Germany: diphenidine is a controlled substance and its production and sale is illegal. Possession is not penalized if intended for self-consumption.
- United Kingdom: it has been illegal to produce, supply or import diphenidine since May 2016.

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

No data.

References


Data were obtained from 105 Member States (19 African Region, 13 Eastern Mediterranean Region, 40 European Region, 16 Region of the Americas, seven South-East Asia Region and 10 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire is 13 (three African Region, two Eastern Mediterranean Region, two European Region, three Region of the Americas, one South-East Asia Region and two Western Pacific Region), leaving 92 active countries. Of these, 32 countries had information on the substance (Table 1).

Table 1. Numbers of countries providing information on DIPHENIDINE

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of countries without information</th>
<th>Number of countries with information on substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa Region</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>European Region</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total 92</strong></td>
<td><strong>60</strong></td>
<td><strong>32</strong></td>
</tr>
</tbody>
</table>

LEGITIMATE USE

No countries reported approved human medical products or veterinary products containing DIPHENIDINE.

One country (Region of the Americas) reported DIPHENIDINE being currently used in medical or scientific research (excluding use as an analytical reference standard), specifically in cell line studies (binding/functional assays) and animal studies.

One country (Region of the Americas) reported DIPHENIDINE being used in industrial or other non-medical or non-scientific use.

No countries reported approved therapeutic indications for DIPHENIDINE.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

Thirteen countries reported that DIPHENIDINE is being misused or abused for its psychoactive properties/recreational use.
The most common known route of administration reported was oral (Table 2).

Table 2. Common routes of administration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>7</td>
</tr>
<tr>
<td>Injection</td>
<td>1</td>
</tr>
<tr>
<td>Inhalation</td>
<td>2</td>
</tr>
<tr>
<td>Sniffing</td>
<td>1</td>
</tr>
<tr>
<td>Smoking</td>
<td>3</td>
</tr>
<tr>
<td>Don’t know</td>
<td>16</td>
</tr>
</tbody>
</table>

The most common known formulation of DIPHENIDINE reported was powder (Table 3).

Table 3. Common formulations reported by countries

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>12</td>
</tr>
<tr>
<td>Tablets</td>
<td>5</td>
</tr>
<tr>
<td>Liquid for oral use</td>
<td>1</td>
</tr>
<tr>
<td>Solution for injection</td>
<td>0</td>
</tr>
<tr>
<td>Don’t know</td>
<td>14</td>
</tr>
</tbody>
</table>

To the above, countries added:
- “herbal mixture”
- “in plant materials together with other substances”.

Nine countries reported the level of negative health impact due to DIPHENIDINE’s non-medical consumption as “serious” or “substantial” (Table 4).

Table 4. Level of negative health impact

<table>
<thead>
<tr>
<th>Serious</th>
<th>Substantial</th>
<th>Negligible</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>5</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

One country (European Region) commented, “… there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers, etc.”.

Five countries (five European Region) reported emergency room admissions related to the non-medical use of DIPHENIDINE.
Concerning reported adverse effects, one country (European Region) noted, “dizziness, coma (Glasgow 6), headache, vomiting, visual and auditory hallucinations, paranoia, dissociation, drowsiness, restlessness, extrapyramidal syndrome, nystagmus”. Another (European Region) noted, “pupils, nystagmus, disorientation, anxiety, agitation, decreased consciousness, hallucinations, high heart rate, high blood pressure, muscle rigidity, cramps, elevated body temperature”. “In combination with other drugs: agitation, confusion, paranoid ideation, suicidal ideation” were noted by another country (European Region).

No countries reported users of DIPHENIDINE presenting for drug dependence treatment.

Regarding mortality, no countries reported deaths involving DIPHENIDINE.

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

Fifteen countries responded that DIPHENIDINE is currently controlled under national legislation to regulate its availability.

Table 5 shows the main reported activities involving DIPHENIDINE.

<table>
<thead>
<tr>
<th>Activities</th>
<th>Number of countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smuggling from other countries</td>
<td>3</td>
</tr>
<tr>
<td>Manufacture of substance by chemical synthesis</td>
<td>1</td>
</tr>
<tr>
<td>Manufacture of substance by extraction from other products</td>
<td>0</td>
</tr>
<tr>
<td>Production of consumer products containing the substance</td>
<td>0</td>
</tr>
<tr>
<td>Trafficking</td>
<td>4</td>
</tr>
<tr>
<td>Diversion from legal supply chain</td>
<td>0</td>
</tr>
<tr>
<td>Internet sales – seller or website located in country</td>
<td>2</td>
</tr>
<tr>
<td>Internet sales – from abroad to buyers in country</td>
<td>2</td>
</tr>
<tr>
<td>Internet sales – other, or location of sellers and website unknown</td>
<td>4</td>
</tr>
<tr>
<td>Direct sales to people who use the substance</td>
<td>1</td>
</tr>
<tr>
<td>Don’t know</td>
<td>17</td>
</tr>
</tbody>
</table>

To the above, countries added:
- “trafficking through postal services”
- “Internet sales (without other information)”
- “probably drug dealing”.

Eight countries (six European Region, one Region of the Americas, one Western Pacific Region) reported seizures (Table 6).
Twenty-four countries have the forensic laboratory capacity to analyse DIPHENIDINE.

One country (European Region) commented, “Forensic laboratories have the capacity to analyse DIPHENIDINE if reference material is available”.

<table>
<thead>
<tr>
<th>Year</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>3</td>
</tr>
<tr>
<td>2019</td>
<td>24</td>
</tr>
<tr>
<td>2018</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
</tr>
</tbody>
</table>