EUDA
EUROPEAN UNION DRUGS AGENCY

Date issued: 31.01.2025

PRECURSOR ASSESSMENT REPORT of phenyl-2-nitropropene

This EUDA Precursor Assessment Report examines the evidence on phenyl-2-nitropropene, evaluating its licit use in the EU and the extent of its use in illicit production. This document was prepared at the request of the European Commission, pursuant to the Regulation (EU) 2023/1322 of the European Parliament and of the Council of 27 June 2023 on the European Union Drugs Agency (EUDA) and repealing Regulation (EC) No 1920/2006 ([1]), particularly the Article 14 (2).

The document available here is a redacted version of the original precursor assessment report. Sections that contain detailed methodology or technical information that could be misused to enable illicit synthesis have been withheld in the interest of public safety. Access to the unredacted report is restricted and will only be provided to verified law-enforcement or regulatory authorities upon request to: precursors@euda.europa.eu

Summary

Evidence

Phenyl-2-nitropropene is a chemical precursor used for the production of amphetamine – a phenethylamine stimulant drug. Amphetamine has been under international control since 1971 It is present on the global drug market in different forms and is one of the most common synthetic stimulants available in Europe.

The quantity of amphetamine seized in the EU remained relatively stable – estimated at between 4 and 6 tonnes per year – until 2019 and 2020, when large amounts of amphetamine-containing captagon tablets were seized in the EU in transit to the Arabian Peninsula. Following a decline from a peak in 2020 (22.3 tonnes), the quantity of the drug seized in the European Union remained stable at about 7 tonnes between 2021 and 2022.

Production of amphetamine in the EU seems to be focused primarily around the Netherlands, Belgium, Poland and Germany. Between 2013 and 2023, at least 1 163 sites have been reported as involved in production or processing of amphetamine in 17 Member States. The number of dismantled sites has been relatively stable over the years, with about 110 sites related to amphetamine production or processing dismantled in Europe every year.

Phenyl-2-nitropropene can be directly converted into amphetamine by a number of different reducing agents through the so called nitrosyrene method. This method is straightforward and scalable, needing only basic equipment and minimal technical proficiency to be executed. Phenyl-2-nitropropene can also

([1]) https://eur-lex.europa.eu/eli/reg/2023/1322/oj

be relatively easily synthetised from benzaldehyde and nitroethane in the presence of catalytic amounts of an amine.

Reports of seizures of phenyl-2-nitropropene in the EU have been registered, however, it is still a non-scheduled substance and reporting is voluntary. Between 2012 and 2024, 42 cases of seizures of phenyl-2-nitropropene have been reported to the EDPD by 10 Member States (Austria, Belgium, Estonia, Finland, Germany, Hungary, Latvia, the Netherlands, Poland and Sweden), totalling over 790 kilograms.

Five incidents occurring in the EU countries, totalling 607 kilograms, were reported to the Precursors Incidents Communication System (PICS) between 2011 and 2017, some of which may be duplicated with data already reported to the EDPD.

When known, shipments of the substance to the EU originated primarily in China and Hong Kong, with destinations including Italy and the Netherlands. Mislabelling was reported in one case. At least ten of the seizures occurred in illicit laboratories, but it is likely that seizures of phenyl-2-nitropropene in illicit production facilities are under-reported.

Phenyl-2-ntropropane has legitimate use as a reference standard for analytical laboratories. It also cannot be ruled out that it is not used for the licit manufacture of amphetamine-based pharmaceutical products.

Scheduling considerations

Scheduling phenyl-2-propiophenone may contribute to reducing the availability of amphetamine in the EU and limit the generation of large profits for organised crime groups. However, the impact of this action would be difficult to assess, as the nitrostyrene method does not appear to be the main method used for amphetamine production. Alternative strategies can also be adopted by illicit drug producers.

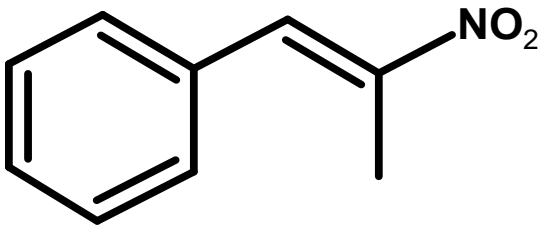
Alternative synthetic routes to produce amphetamine include the Leuckart method, using benzyl methyl ketone (BMK, P-2-P) or its pre-precursors. The reaction of BMK with formamide affords an intermediate, which reacted with hydrochloric acid affords the racemic amphetamine oil. This is the method predominantly used to produce amphetamine in the European Union.

Illicit amphetamine producers could also shift the production to other products, for example synthetic cathinone stimulants, which might produce similar effects to amphetamine and can be easily synthesised from non-scheduled precursor chemicals.

Scheduling phenyl-2-propiophenone is unlikely to impact legitimate industries, as the substance appears to have no known legitimate use in the sources consulted, outside of its use as a reference standard for analytical laboratories. However, it could not be ruled out that phenyl-2-nitropropene is not used in the legitimate manufacture of amphetamine-based pharmaceutical products.

These factors should be weighed against the risks of not scheduling of the substance. If phenyl-2-propiophenone remains freely available, some illicit drug producers may be enabled to continue producing amphetamine in EU territory. This has the potential to increase potential health risks associated with amphetamine use and the risk of generating large profits for organised crime groups.

1. Substance description

PAR_ID	2025-0009
Substance name	Phenyl-2-nitropropene
Abbreviation	P2NP
Chemical structure	
IUPAC name	[(E)-2-nitroprop-1-enyl]benzene
InChI code	InChI=1S/C9H9NO2/c1-8(10(11)12)7-9-5-3-2-4-6-9/h2-7H,1H3
InChI Key	WGSVFWFSJDAYBM-UHFFFAOYSA-N
SMILES	C(=C(N(=O)=O)C)C1=CC=CC=C1
Other names	(2-Nitropropenyl)benzene; 1-Phenyl-2-nitropropene
Molecular formula	$C_9H_9NO_2$
Molecular weight (g/mol)	163.17
EUDA Classification	Other
CAS RN	705-60-2
CAS page link	https://commonchemistry.cas.org/detail?cas_rn=705-60-2&search=1-Phenyl-2-nitropropene
HS/CN code	29042000
TARIC link	https://ec.europa.eu/taxation_customs/dds2/taric/measures.jsp?Lang=en&SimDate=20240912&Area=&MeasType=&StartPub=&EndPub=&MeasText=&GoodsText=&op=&Taric=29042000&AdditionalCode=&search_text=goods&textSearch=&LangDescr=en&OrderNum=&Regulation=&measStartDat=&measEndDat=&DatePicker=12-09-2024
CUS number (ECICS)	0152463-6
ECICS link	N/A
EC number	627-363-3
REACH link	https://echa.europa.eu/substance-information/-/substanceinfo/100.155.731
Physical form (RT)	Solid, crystalline substance
Colour	Yellow

Physical features	Distinct smell
Associated with the production of	Amphetamine
GHS Hazard Statements	H335 - May cause respiratory irritation H319 - Causes serious eye irritation H315 - Causes skin irritation H302 - Harmful if swallowed

2. Evidence of use in the illicit production

2.1 Background

Phenyl-2-nitropropene is a nitrostyrene compound, i.e., an arylnitroalkene that consists a phenyl group attached to an ethene chain with at least one nitro group (-NO_2) attached either to the phenyl ring or the alkene group. In the case of phenyl-2-nitropropene, the nitro group is attached in the second carbon of the propene chain. According to the published literature (DeRuiter et al., 1994), **phenyl-2-nitropropene** is associated with the illicit production of **amphetamine,** a phenethylamine stimulant drug.

Phenethylamines are a group of synthetic stimulant substances which also include methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA). Some of these compounds, including amphetamine and its enantiomers, have found applications as medicines and are legally marketed around the world.

Amphetamine exists in two chemical forms, base and salt. The pure base is a clear, colourless oil that is insoluble in water and can easily be converted into a water-soluble salt. The most common salt form on the European market is amphetamine sulfate (EMCDDA and Europol, 2023b). Amphetamine also exists in two chiral forms (where the arrangement of atoms in the molecule are slightly different): *d*-amphetamine (dextroamphetamine) and *l*-amphetamine (levoamphetamine), with the latter one being less potent. Amphetamine sulfate is a white or off-white powder that is soluble in water.

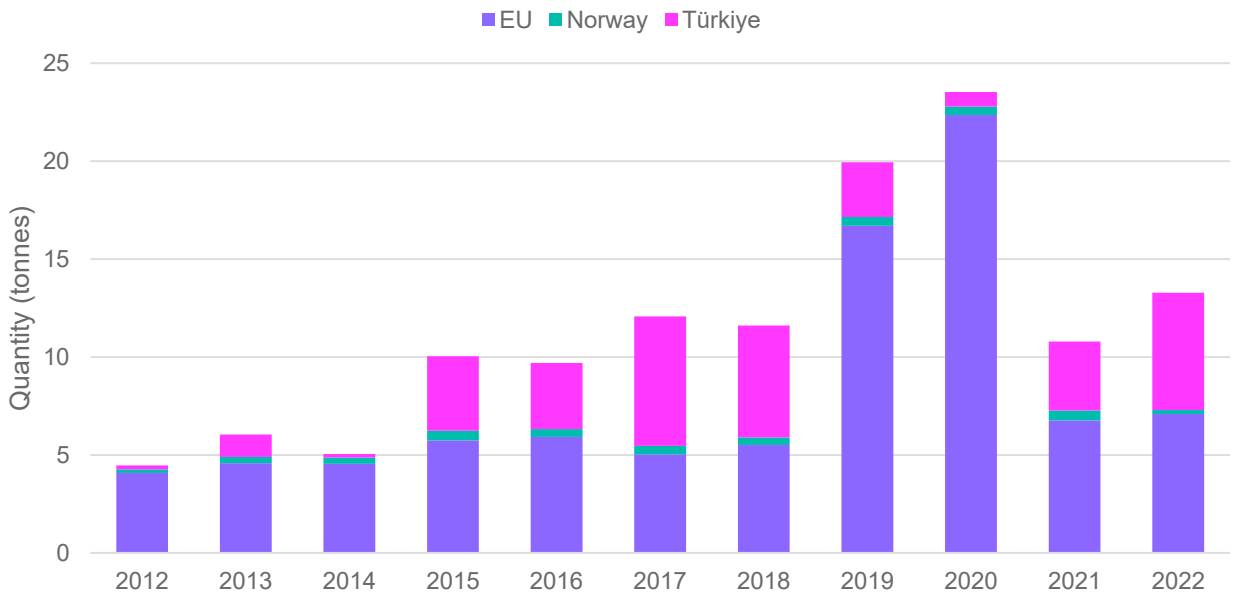
Amphetamine has a long presence on the EU drug market (EMCDDA and Europol, 2023b). Both amphetamine and dextroamphetamine are internationally controlled in Schedule II of the 1971 Convention on Psychotropic Substances and were included in the original draft of the Convention. Levoamphetamine has been added to the Schedule II of the 1971 Convention in 1986.

At the global level, criminals operating in the European Union are key producers of illicit amphetamine (EMCDDA and Europol, 2023b). The amphetamine consumed in the EU is believed to be exclusively produced locally, with production concentrated in the Netherlands and Belgium. In some cases, the manufacturing of the consumer product is not completed in these countries and the amphetamine base oil is exported to another country, where it is converted into amphetamine sulfate (salt). A much smaller proportion of the amphetamine produced by criminals operating in the EU is used to make captagon tablets, a popular form of the drug consumed mainly in the Arabian Peninsula. These typically contain amphetamine, caffeine and occasionally theophylline, and display a characteristic logo of two half-moons (EMCDDA and BKA, 2023). Large scale seizures of millions of captagon tablets have been reported in Europe, particularly in Greece in 2019 ([2]) and in Italy in 2020 ([3]), with both of these seizures

([2]) https://www.ekathimerini.com/news/242107/piraeus-counterfeit-captagon-amphetamine-haul-in-the-millions/
([3]) https://www.reuters.com/article/world/italian-police-seize-record-amount-of-amphetamines-shipped-from-syria-idUSKBN2425EF/

being reflected on Figure 1. The increase in seizures of captagon tablets has been especially seen in Türkiye, but has also reported by many EU countries (EMCDDA and BKA, 2023).

Figure 1. Quantity (tonnes) of amphetamine seized in the EU (2012-2022)



Source: European Drug Report, 2024

Based on the data reported to the EUDA and Europol, in 2022, 7 EU Member States reported dismantling 108 amphetamine laboratories (119 in 2021): the Netherlands (39), Belgium (35), Poland (22), Spain (5), Sweden (5), Croatia (1) and Romania (1) (EMCDDA and Europol, 2024). The number of dismantled sites has been relatively stable over the years, with about 110 sites related to amphetamine processing dismantled in Europe every year, however, the size and production capacity of some these facilities appear to have increased significantly over the years, partly facilitated by the bulk availability of drug precursors.

Data on the quantity and the identity of precursors seized at these sites is not routinely recorded in any of the data sources available. Nonetheless, in the large majority of cases BMK (benzyl methyl ketone, also known as P-2-P) was indicated as the precursor chemical used for amphetamine synthesis. In almost half of the cases the precursor used on the site was not known or not reported. In a small percentage of all reports the indicated precursor was phenyl-2-nitropropene Those cases were largely reported by Poland. Other precursors were also mentioned in some of the reports.

2.2 General methods for the synthesis of amphetamine

Multiple methods exist for the synthesis of amphetamine (EMCDDA and Europol, 2023b). Amphetamine is usually present on the market in its racemic form (i.e., a 1:1 mixture of *d*-amphetamine and *l*-amphetamine) (Losacker et al., 2022), therefore the synthesis does not need to be stereoselective, nor

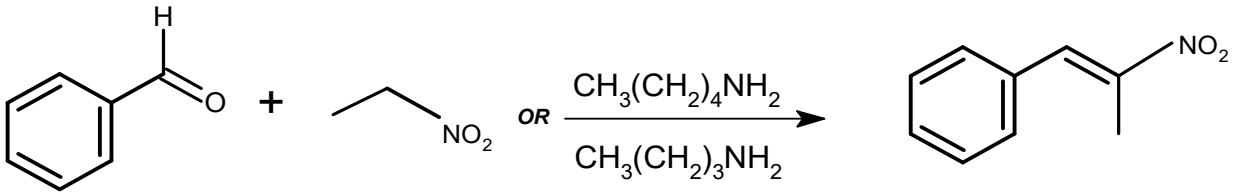
does the final product need to be recycled to produce an enantiomerically pure substance, as in the case of methamphetamine (EMCDDA and Europol, 2022).

2.2.1 Nitrostyrene method

The nitrostyrene method appears to be less common than the Leuckart method (See 2.2.2) for the production of amphetamine in the EU. The first step of the nitrostyrene method usually starts with the synthesis of phenyl-2-nitropropene (P2NP) from benzaldehyde and nitroethane in the presence of catalytic amounts of an amine (via a standard Knoevenagel reaction) (Scheme 1) (DeRuiter et al., 1994). If isolated, this substance is a bright yellow crystalline solid with a distinctive smell, soluble in acetone, chloroform, dichloromethane and methanol.

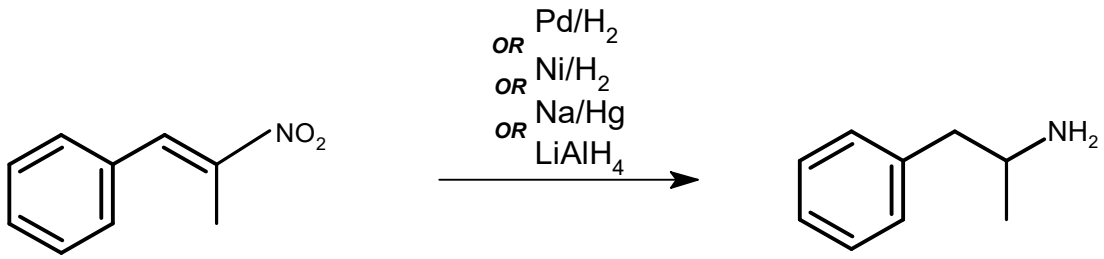
Phenyl-2-nitropropene is also commercially available from chemical suppliers, meaning that the first step can be omitted and the synthesis can start directly form the second step (Scheme 2). Phenyl-2-nitropropene can be converted into amphetamine oil by a number of reduction techniques, including the use of a reducing agent, such as lithium aluminium hydride (LAH), sodium amalgam, Raney nickel (Ni) or palladium (Pd) catalyst. Platinum (Pt) in the form of Adams' catalyst can also be used. The amphetamine oil is then usually converted into amphetamine sulfate through a reaction with sulfuric acid (EMCDDA and Europol, 2024).

Scheme 1 Phenyl-2-nitropropene synthesis



benzaldehyde nitroethane phenyl-2-nitropropene

Scheme 2 Nitrostyrene method for amphetamine synthesis



phenyl-2-nitropropene amphetamine

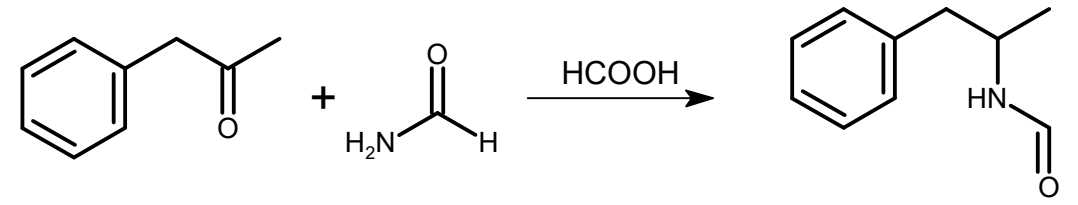
Phenyl-2-nitropropene can also be reduced to BMK (P-2-P), the precursor in the synthesis of amphetamines in the below-described Leuckart method. To perform the reduction, sodium borohydride can be used, followed by hydrolysis of the nitro group with hydrogen peroxide and potassium carbonate to produce phenyl-2-propanone. In another method, iron is the reducing agent and hydrochloric acid or acetic acid are used as catalysts forming an intermediate which hydrolyses into phenylacetone as well (DeRuiter et al., 1994; Toske et al., 2019). Although it has been described in literature and suspected to be occasionally used for methamphetamine production in the US based on impurity profiling (Toske et al., 2019), so far this phenomenon has not been reported by any EU Member State.

2.2.2 Leuckart method

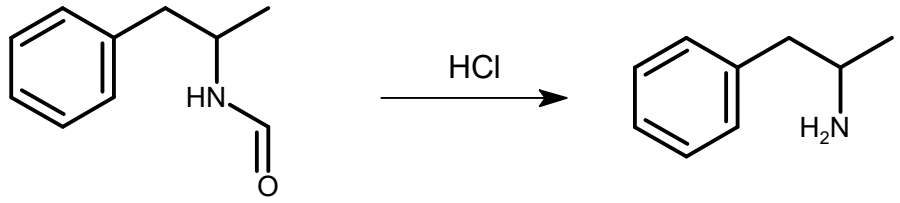
The most commonly used method for the synthesis of amphetamine the Leuckart method. The Leuckart method is a relatively simple, versatile and well-established organic chemistry process that converts carbonyl compounds (aldehydes or ketones) into amines, under heating. This method may also be used in the synthesis of methamphetamine, MDMA, MDA and a number of other compounds, depending on what carbonyl and amine combination is used. Despite being a procedure that does not require a high level of skill or a complicated set-up, it is labour intensive, requires the use of high temperatures (around 190 ºC in some cases) and, compared to the methods used for the production of other synthetic drugs, is associated with relatively low production yields (EMCDDA and Europol, 2023b).

Typically, the Leuckart synthesis of amphetamine begins with heating BMK (P-2-P) with formamide, often in the presence of formic acid, to form an intermediate *N*-formylamphetamine (*N*-FA) (see Scheme 3). is then converted to racemic amphetamine base oil using hydrochloric acid. After this step, sodium hydroxide is usually added to separate the amphetamine base, in the form of crude oil, which is subsequently purified by distillation, or, less frequently, by solvent extraction. In the final step the purified base oil is then reacted with sulfuric acid to afford the final product amphetamine sulfate (EMCDDA and Europol, 2023b).

Scheme 3 General scheme of the Leuckart method used for the illicit amphetamine production



BMK (P-2-P) formamide *N*-formylamphetamine



N-formylamphetamine amphetamine

Because BMK is an internationally controlled precursor, it may often be produced in Europe from alternative chemicals, such as APAAN, glycidic derivatives of BMK, APAA and MAPA, all of which were successively introduced in the market as legal controls were applied to their predecessors (EMCDDA and Europol, 2022).

3. Evidence of trafficking in the EU

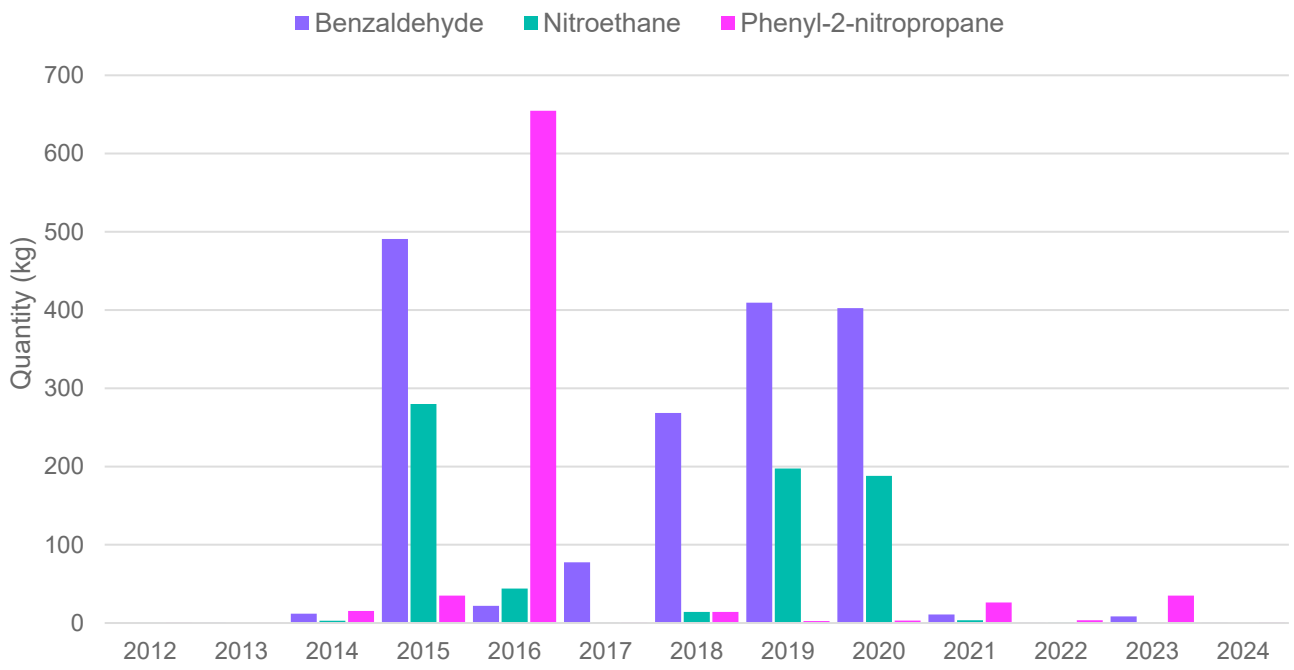
Phenyl-2-nitropropene is not a scheduled precursor and thus the reporting of its seizures and stopped shipments to the European Drug Precursors Database (EDPD) is voluntary at this point. Its legal status is likely to result in its de-prioritization in law enforcement activity and therefore data may not be recorded or reported (Singleton et al, 2018).

Between 2012 and 2024, 42 cases of seizures of phenyl-2-nitropropene have been reported to the EDPD by 10 Member States (Austria, Belgium, Estonia, Finland, Germany, Hungary, Latvia, the Netherlands, Poland and Sweden), totalling over 790 kilograms. The biggest of these seizures was reported by Belgium in 2016, when 604 kg were seized in a shipment originating from Hong Kong, destined to Italy. The same year 50 kg of phenyl-2-nitropropene were seized in Belgium originating in China, destined to the Netherlands.

The origin and/or provenance was reported in 5 out of 42 reports (corresponding to 656 kg out of the 790 kg of material seized). In two of the cases for which it was known, the origin was China, and in two cases in Estonia the shipment had come from Spain (small quantities). Another case reported by Estonia indicated the origin as Poland.

Seizures of phenyl-2-nitropropene and the substances used for its synthesis – benzaldehyde and nitroethane (Scheme 1), have been reported in the EU (Figure 2). It should be noted, however, that seizures of precursors needed to synthesise amphetamine via the Leuckart method have dominated throughout the same time period (EMCDDA and Europol, 2023b).

Figure 2. Quantity of amphetamine precursors used in the nitrostyrene method seized in the EU, EU Drug Precursors Database, 2024



4. Legitimate uses in the EU

Phenyl-2-nitropropene is commercially available as a reference standard used in analytical laboratories ([4]). No information about its legal trade has been found in the ECHA database.

Even though phenyl-2-nitropropene does not seem to be traded in the EU, it cannot be ruled out that it is not used for legitimate production of pharmaceutical amphetamine outside of Europe. It appears that phenyl-2-nitropropene has certain applications in medicinal chemistry and organic synthesis. The full extent of its applications in scientific research would be difficult to evaluate, and it is not the subject of this report.

Amphetamine-containing medicines are not authorised for use in the EU, with the exception of Lisdexamfetamine (sold under the brand names Vyvanse, Elvanse, and others) for the treatment of attention deficit hyperactivity disorder (ADHD). Lisdexamfetamine is an inactive prodrug that is converted to dextroamphetamine in the body. Chemically, it is a substituted amphetamine with an amide linkage to the essential amino acid L-Lysine, making the drug less prone to abuse. However, amphetamine-based preparations used for treatment of ADHD are marketed in other parts of the world (e.g., a 1:1 amphetamine/dextroamphetamine salt mixture sold under the brand name Adderall in the US). Due to limited information available on the method of pharmaceutical preparation of that and other amphetamine-containing pharmaceutical products, it is possible that they may be produced from phenyl-2-nitropropene.

According to the information provided by the INCB through the assessments of annual medical and scientific requirements for substances listed in Schedule II, III and IV of the 1971 Convention on Psychotropic Substances, the expected requirements for the EU in 2025 of dexamphetamine are around 14.6 tonnes, amphetamine 82 kilograms, and levamfetamine 1.4 kilograms. The highest requirements for dextroamphetamine in the EU countries were reported by Croatia (7 tonnes), Denmark (5 tonnes) and Germany (2 tonnes). For amphetamine, France reported the requirements of 30.1 kilograms, Germany of 17.7 kilograms, and Sweden of 15 kilograms. The non-EU requirements for dexamphetamine are around 26.7 tonnes, amphetamine 24.1 tonnes, and levamfetamine 1.1 kilograms, with the majority of the quantity required by the USA (22.1 tonnes of dexamphetamine, 21.2 tonnes of amphetamine and 30 kilograms of levamfetamine).

5. Legal controls

Based on the available information, phenyl-2-nitropropene is not a controlled substance in any of the searched jurisdictions ([5]), except for Taiwan. In Taiwan, it is controlled under the Schedule 4 Controlled Drug Materials, Controlled Drugs Act (Item 42). Various other amphetamine (and methamphetamine) precursors are scheduled under the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988, including ephedrine, pseudoephedrine, phenylacetic acid, 1-phenyl-2-propanone (P-2-P, BMK), P-2-P methyl glycidic acid (“BMK glycidic acid”) and its selected

([4]) https://www.caymanchem.com/product/22185#reference63022
([5]) Searched jurisdictions and treaties: Argentina, Austria, Belgium, Brazil, Canada, Chemical Weapons Convention, Australia Group, China, Denmark, European Union, Finland, France, Germany, India, Indonesia, Ireland, Italy, Japan, Mexico, Montreal Ozone Protocol, Netherlands, Norway, Poland, Rotterdam Convention, Saudi Arabia, Singapore, Slovakia, Spain, Sweden, Switzerland, Taiwan, UN (INCB), United Kingdom, United States of America, Wassenaar Arrangement, World Anti-Doping Agency.

esters ([6]), methyl alpha-phenylacetoacetate (MAPA), alpha-phenylacetoacetamide (APAA) and alpha-phenylacetoacetonitrile (APAAN).

In addition to the substances scheduled in the UN Conventions, in the EU additional amphetamine precursors ethyl alpha-phenylacetoacetate (EAPA) and diethyl (phenylacetyl) propanedioate (DEPAPD) are also controlled ([7]).

6. Use, trafficking and distribution outside of the EU

[This section was redacted]

7. Conclusions and possible consequences of scheduling in the EU

The limited seizure data available suggests that phenyl-2-nitropropene is used in the European Union as a precursor in the synthesis of amphetamine, but production of amphetamine using the nitrostyrene method has rarely been reported in Europe, with the exception of Poland. In Europe, seizures of precursors and essential chemicals associated with the nitrostyrene method are minor compared to those associated with the Leuckart method. A possible reason for this may be that the chemicals needed for the nitrostyrene method are widely used in various industries. (EMCDDA and Europol, 2023b). When the nitrostyrene method is used, it appears that often the phenyl-2-nitropropene is first produced from benzaldehyde and nitroethane. However, indications of direct synthesis from phenyl-2-nitropropene have also been found. This is likely to be motivated by an attempt to simplify the synthesis procedure to one step and avoid using controlled precursors such as BMK and its pre-precursors.

Scheduling of phenyl-2-nitropropene may lead to unpredictable outcomes. Some of the potential scenarios are listed below:

- ***Scheduling phenyl-2-nitropropene may contribute to reducing the availability of amphetamine in the EU.*** Inclusion of the chemical under EU controls might make its trade and use for illicit production of amphetamine more difficult and, thus, contribute to reducing the availability of amphetamine in the EU. However, phenyl-2-nitropropene does not appear to be the main precursor in illicit production of amphetamine, as the production from the scheduled substances BMK or its pre-precursors is the dominant method. Therefore, the impact of scheduling would be difficult to assess. Nevertheless, following the ban, the illicit production might shift to other starting materials, different synthetic routes or other end-products altogether.

- ***Scheduling phenyl-2-nitropropene may result in different chemical routes being adapted by illicit drug producers in the EU.*** Numerous alternative synthetic methods for amphetamine exist which avoid phenyl-2-nitropropene and could potentially be used for production in case of its scheduling. The most relevant one is the Leuckart method (Scheme 3).

- ***Scheduling 2 phenyl-2-nitropropene may result in the emergence of additional 'designer' amphetamine precursors in the EU.*** The scheduling of phenyl-2-nitropropene may motivate

([6]) Methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl esters of P-2-P methyl glycidic acid.
([7]) under Council Regulation (EC) No 111/2005 of 22 December 2004 laying down rules for the monitoring of trade between the Union and third countries in drug precursors http://data.europa.eu/eli/reg/2005/111/2024-06-03 and Regulation (EC) No 273/2004 of the European Parliament and of the Council of 11 February 2004 on drug precursors (Text with EEA relevance) http://data.europa.eu/eli/reg/2004/273/2024-06-03

illicit drug producers to seek alternatives to the precursor, or, additionally, import 'masked' alternatives of the final product. [This section was redacted in the interest of public safety]

- ***Scheduling phenyl-2-nitropropene may shift illicit drug production to different end-products.*** Lack of access to the precursor necessary to produce amphetamine could result in the shift of illicit production to other types of stimulant substances, including synthetic cathinones for which the precursors are not currently controlled.

- ***Scheduling of 2 phenyl-2-nitropropene is unlikely to impact legitimate industries in the EU*****,** as the substance appears to have limited legitimate use in the EU. However, it was impossible to rule out that it is not used for the legitimate manufacture of pharmaceutical amphetamine in other parts of the world.

The information above appears to indicate that there are some risks to be considered concerning the scheduling of phenyl-2-nitropropene. These should be weighed against the risks of not scheduling the substance.

Not scheduling phenyl-2-nitropropene may enable illicit drug producers to continue producing amphetamine in EU territory**.** Amphetamine has an established presence on the EU drug market. Surveys conducted by 24 EU countries between 2017 and 2023, which group amphetamine and methamphetamine together, suggest that 1.5 million young adults (15 to 34) used amphetamines during the last year (1.5 % of this age group) (EMCDDA, 2024).

In addition, the production and trafficking of amphetamine generates large profits for organised crime groups. It is estimated that the overall minimum value of the EU amphetamine retail market is EUR 1.1 billion, with a range of EUR 0.9 billion to EUR 1.4 billion. Estimates of the amounts used suggest that about 90 tonnes of amphetamine and methamphetamine combined (likely range: 70 to 107 tonnes) was consumed in the EU in 2021 (EMCDDA and Europol, 2022).

Additional unintentional consequences may also occur due to a range of factors, derived from currently unpredictable market dynamics. This document should be viewed as part of a broader decision-making process, requiring ongoing evaluation as circumstances evolve.

8. References

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