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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1310

[Docket No. DEA-1189]

Propionyl Chloride

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Advanced notice of proposed rulemaking.

SUMMARY: The Drug Enforcement Administration finds that propionyl chloride is used in the illicit manufacture of the controlled substance fentanyl, as well as fentanyl analogues, and fentanyl-related substances and is important to the manufacture of these substances because it is often used in synthetic pathways to illicitly manufacture fentanyl, fentanyl analogues, and fentanyl-related substances. Prior to proposing to list propionyl chloride as a list I chemical, DEA is soliciting information on the current uses of propionyl chloride (other than for the synthesis of fentanyl) in order to properly determine the effect such a proposed action would have on legitimate industry.

DATES: Comments must be submitted electronically or postmarked on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. Commenters should be aware that the electronic Federal Docket Management System will not accept any comments after 11:59 p.m. Eastern Time on the last day of the comment period.

ADDRESSES: To ensure proper handling of comments, please reference "Docket No. DEA-1189" on all electronic and written correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration (DEA) encourages that all comments be submitted electronically through the Federal eRulemaking Portal which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to

https://www.regulations.gov and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on *Regulations.gov*. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.

- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary. Should you wish to mail a paper comment, *in lieu of* an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362–3249.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received in response to this docket are considered part of the public record. They will, unless reasonable cause is given, be made available by DEA for public inspection online at *https://www.regulations.gov.* Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase "PERSONAL IDENTIFYING INFORMATION" in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made

publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase "CONFIDENTIAL BUSINESS INFORMATION" in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information or confidential business information identified as directed above will be made publicly available in redacted form. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to *https://www.regulations.gov* may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this advanced proposed rule is available at *https://www.regulations.gov* for easy reference.

Legal Authority

The Controlled Substances Act (CSA) gives the Attorney General the authority to specify, by regulation, chemicals as list I chemicals.[1] A "list I chemical" is a chemical that is used in manufacturing a controlled substance in violation of the CSA and is important to the manufacture of the controlled substances.[2] The current list of all listed chemicals is published at 21 CFR 1310.02. Pursuant to 28 CFR 0.100(b), the Attorney General has delegated his authority to designate list I chemicals to the Administrator of DEA (Administrator). DEA regulations set forth the process by which DEA may add a chemical

[1] 21 U.S.C. 802(34).
[2] Id.

as a listed chemical. As set forth in 21 CFR 1310.02(c), the agency may do so by publishing a final rule in the Federal Register following a published notice of proposed rulemaking with at least 30 days for public comments.

Background

The clandestine manufacture of fentanyl, fentanyl analogues, and fentanyl-related substances remains extremely concerning as the distribution of illicit fentanyl, fentanyl analogues, and fentanyl-related substances continues to drive drug-related overdose deaths in the United States. Fentanyl is a synthetic opioid and was first synthesized in Belgium in the late 1950s. Fentanyl was introduced into medical practice and is approved for medical practitioners in the United States to prescribe lawfully for anesthesia and analgesia. Yet, due to its pharmacological effects, fentanyl can be used as a substitute for heroin, oxycodone, and other opioids in opioid dependent individuals. Therefore, despite its accepted medical use in treatment in the United States, DEA controls fentanyl as a schedule II controlled substance due to its high potential for abuse and dependence.[3] Moreover, there are a substantial number of fentanyl analogues and fentanyl-related substances that are being distributed on the illicit drug market despite DEA's actions adding them as schedule I controlled substances. Illicit manufacturers attempt to utilize unregulated precursor chemicals to evade law enforcement detection and precursor chemical controls in order to manufacture fentanyl, fentanyl analogues, and fentanyl-related substances. This strategy allows for the synthesis of a variety of fentanyl analogues and fentanyl-related substances by making slight modifications to the core fentanyl structure while maintaining the same synthetic methodology used to synthesize fentanyl, fentanyl analogues, and fentanyl-related substances.

The unlawful trafficking of fentanyl, fentanyl analogues, and fentanyl-related substances in the United States continues to pose an imminent hazard to the public safety. Since 2012,

[3] 21 U.S.C. 812(c) Schedule II(b)(6) and 21 CFR 1308.12(c).

fentanyl has shown a dramatic increase in the illicit drug supply as a single substance, in mixtures with other illicit drugs (*i.e.*, heroin, cocaine, and methamphetamine), and in forms that mimic pharmaceutical preparations including prescription opiates and benzodiazepines.[4]

DEA has noted a significant increase in overdoses and overdose fatalities from fentanyl, fentanyl analogues, and fentanyl-related substances in the United States in recent years. According to the Centers for Disease Control and Prevention (CDC), opioids, mainly synthetic opioids (which includes fentanyl), are predominantly responsible for drug overdose deaths in recent years. According to CDC WONDER,[5] drug-induced overdose deaths involving synthetic opioids (excluding methadone) in the United States increased from 36,359 in 2019 to 56,516 in 2020 to 70,601 in 2021. Based on provisional data, the predicted number of drug overdose deaths involving synthetic opioids (excluding methadone) in the United States for the 12 months ending October 2022 is 73,570 individuals, or approximately 68 percent of all drug-induced overdose deaths for that time period.[6] The increase in overdose fatalities involving synthetic opioids coincides with a dramatic increase in law enforcement encounters of fentanyl, fentanyl analogues, and fentanyl-related substances. According to the National Forensic Laboratory Information System (NFLIS-Drug),[7] reports from forensic laboratories of drug items containing fentanyl, fentanyl analogues, and fentanyl-related substances increased dramatically since 2014, as shown in Table 1.

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[4] United Nations Office on Drugs and Crime, Global SMART Update Volume 17, March 2017. https://www.unodc.org/documents/scientific/Global_SMART_Update_17_web.pdf.

[5] Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Provisional Mortality on CDC WONDER Online Database. Data are from the final Multiple Cause of Death Files, 2018-2021, and from provisional data for years 2022-2023, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at https://wonder.cdc.gov/mcd-icd10-provisional.html on March 16, 2023.

[6] Ahmad FB, Cisewski JA, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2023. Accessed at https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm on March 15, 2023.

[7] The National Forensic Laboratory Information System (NFLIS-Drug) is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by Federal, State and local forensic laboratories in the United States. While NFLIS-Drug data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332 (December 12, 2011). NFLIS-Drug data was queried on July 31, 2023.

Table 1. Annual Reports of Fentanyl and Select Fentanyl Analogues and Fentanyl-Related Substances Identified in Drug Encounters.

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022
Annual Fentanyl Reports	5,554	15,461	37,154	61,640	89,966	108,131	125,999	164,890	165,067
Annual Reports of select fentanyl analogues and fentanyl-related substances	78	2,317	7,624	21,980	16,177	20,917	7,800	26,368	29,404

Role of Propionyl Chloride in the Synthesis of Fentanyl

Fentanyl, fentanyl analogues, and fentanyl-related substances are not naturally occurring substances. As such, the manufacture of these substances requires them to be produced through synthetic organic chemistry. Synthetic organic chemistry is the process in which a new organic molecule is created through a series of chemical reactions, which involve precursor chemicals. Through chemical reactions, the chemical structures of precursor chemicals are modified in a desired fashion. These chemical reaction sequences, also known as synthetic pathways, are designed to create a desired substance. Several synthetic pathways to fentanyl, fentanyl analogues, and fentanyl-related substances have been identified in clandestine laboratory settings; these include the original "Janssen method," the "Siegfried method," and the "Gupta method." In response to the illicit manufacture of fentanyl, fentanyl analogues, and fentanyl-related substances using these methods, DEA controlled *N*-phenethyl-4-piperidone (NPP),[8] *N*-(1-benzylpiperidin-4-yl)-*N*-phenylpropionamide (benzylfentanyl), *N*-phenylpiperidin-4-amine (4-anilinopiperidine;

[8] 72 FR 20039 (April 23, 2007).

including its amides and carbamates),[9] and 4-piperidone (piperidin-4-one)[10] as list I chemicals and 4-anilino-*N*-phenethylpiperidine (ANPP)[11] and *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl)[12] as schedule II immediate precursors under the CSA.

In 2017, the United Nations Commission on Narcotic Drugs placed NPP and ANPP in Table I of the Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 (1988 Convention) in response to the international reintroduction of fentanyl on the illicit drug market. As such, member states of the United Nations are required to regulate these precursor chemicals at the national level. Importantly, the People's Republic of China regulated NPP and ANPP on February 1, 2018.[13] Subsequently in 2022, the United Nations Commission on Narcotic Drugs placed norfentanyl, 1-boc-4-anilinopiperidine, and 4-anilinopiperidine in Table I of the 1988 Convention in response to the international reintroduction of fentanyl on the illicit drug market and the introduction of new precursors used in the illicit manufacture of fentanyl.

Propionyl Chloride

The original published synthetic pathway to fentanyl, known as the Janssen method, involves the list I chemical benzylfentanyl and schedule II immediate precursor norfentanyl. In this synthetic pathway, benzylfentanyl, a list I chemical under the CSA,[14] is synthesized by reacting propionyl chloride with 4-anilino-1-benzylpiperidine, which is then converted to norfentanyl, the schedule II immediate precursor in this synthetic pathway.[15] Norfentanyl is then subjected to one simple chemical reaction to complete the synthesis of fentanyl. This synthetic pathway can also be easily modified to produce fentanyl analogues and fentanyl-related substances.

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[9] 85 FR 20822 (May 15, 2020).
[10] 88 FR 21902 (May 12, 2023).
[11] 75 FR 37295 (August 30, 2010).
[12] 85 FR 21320 (May 18, 2020).
[13] https://www.dea.gov/press-releases/2018/01/05/china-announces-scheduling-controls-two-fentanyl-precursor-chemicals. Accessed March 9, 2022.
[14] 85 FR 20822 (May 15, 2020).
[15] 85 FR 21320 (May 18, 2020).

Propionyl chloride also serves as a precursor chemical in the Siegfried method. In this synthetic pathway, propionyl chloride is reacted with ANPP,[16] the schedule II immediate precursor in the Siegfried method, to complete the synthesis of fentanyl. This synthetic pathway can also be easily modified to produce fentanyl analogues and fentanyl-related substances.

In addition to the Janssen and Siegfried methods, clandestine manufacturers are using other methods to synthesize fentanyl, one of which is known as the Gupta method. In this synthetic pathway, 4-piperidone, a list I chemical under the CSA, is used to synthesize 4-anilinopiperidine, another list I chemical under the CSA,[17] which serves as an alternative precursor chemical to NPP, a list I chemical, in the synthesis of ANPP, a schedule II immediate precursor albeit through a different synthetic process. The resulting ANPP is reacted with propionyl chloride to manufacture the schedule II controlled substance, fentanyl. This synthetic pathway can also be easily modified to produce fentanyl analogues and fentanyl-related substances.

Propionyl chloride is attractive to illicit manufacturers because of the lack of regulations on this chemical, it is readily available from chemical suppliers, and it can be easily used in many known synthetic pathways used in the illicit manufacture of fentanyl, fentanyl analogues, and fentanyl-related substances.

Solicitation for Information

With this advanced notice of proposed rulemaking, DEA is soliciting information on any possible legitimate uses of propionyl chloride unrelated to fentanyl production (including industrial uses) in order to assess the potential economic impact of controlling propionyl chloride as a list I chemical. DEA seeks to document any unpublicized use(s) and other

[16] 75 FR 37295 (August 30, 2010).
[17] 85 FR 20822 (May 15, 2020).

proprietary use(s) of propionyl chloride that are not in the public domain. Therefore, DEA is soliciting comment on the uses of propionyl chloride in the legitimate marketplace.

DEA is soliciting input from all potentially affected parties regarding: (1) The types of legitimate industries using propionyl chloride; (2) the legitimate uses, legitimate needs and quantity produced, used, and distributed of propionyl chloride; (3) the size of the domestic market for propionyl chloride; (4) the number of manufacturers of propionyl chloride; (5) the number of distributors of propionyl chloride; (6) the level of import and export of propionyl chloride; (7) the potential burden that controlling propionyl chloride as a list I chemical may have on any legitimate industry and trade; (8) the potential number of individuals/firms that may be adversely affected by such regulatory controls (particularly with respect to the impact on small businesses); and (9) any other information on the manner of manufacturing, distribution, consumption, storage, disposal, and uses of propionyl chloride by industry and others. DEA invites all interested parties to provide any information on any legitimate uses of propionyl chloride in industry, commerce, academia, research and development, or other applications. DEA seeks both quantitative and qualitative data.

Such information may be submitted electronically to the address listed above and is requested by [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. This information will be used to properly determine the effect that proposed regulations to make propionyl chloride a list 1 chemical under the CSA would have on industry.

Handling of Confidential or Proprietary Information

Confidential or proprietary information may be submitted as part of a comment regarding this advanced notice of proposed rulemaking. Please see the "POSTING OF PUBLIC COMMENTS" section above for a discussion of the identification and redaction of confidential business information and personally identifying information.

Regulatory Analyses

This ANPRM was developed in accordance with the principles of Executive Order (E.O.) 12866, "Regulatory Planning and Review" and E.O. 13563, "Improving Regulation and Regulatory Review." Since this action is an ANPRM, the requirement of E.O. 12866 to assess the costs and benefits of this action does not apply.

Furthermore, the requirements of the Regulatory Flexibility Act do not apply to this action because, at this stage, it is an ANPRM and not a "rule" as defined in 5 U.S.C. 601. Following review of the comments received in response to this ANPRM, if DEA proceeds with a notice of proposed rulemaking regarding this matter, DEA will conduct all relevant analyses as required by statute or E.O.

SIGNING AUTHORITY

This document of the Drug Enforcement Administration was signed on October 5, 2023, by Administrator Anne Milgram. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the Federal Register.

Heather Achbach,
Federal Register Liaison Officer,
Drug Enforcement Administration.

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