

Illicit Fentanyl: A Perfect Storm in Science

Donna J. Nelson*

Department of Chemistry, University of Oklahoma, Norman, OK 73019

Abstract: Characteristics, uses, and impacts of illicit fentanyl upon society have combined to create a perfect storm in science. In recent years, fentanyl has been responsible for almost 210,000 poisonings in the US, with hundreds of people dying each day, and the number is rapidly growing. More research to understand better and to increase illicit fentanyl mitigation, such as naloxone and vaccination, is needed. Confidence in literature data and results is necessary in order to inspire scientists to enter a field, but fentanyl has displayed anomalies in its chemical behavior and has experienced anomalies in its data compilation and analysis, which has made it confusing and daunting.

Introduction

An increasing number of news reports of U.S. illicit fentanyl poisonings reveals our growing opioid crisis. Almost 210,000 people died from illicit fentanyl in the years 2015 – 2021.[1] In six states, illicit fentanyl fatalities recently increased by almost a factor of 5 in only 2 years. [1] Fentanyl is the leading cause of death for U. S. adults aged 18–45.[1,2] Synthetic opioid (fentanyl) fatalities among children are rising faster than in any other age group, and these tripled in just two years.[1] More research to understand better and to increase illicit fentanyl mitigation, such as naloxone and vaccination,[3] is needed. Much effort has been expended to reduce illicit fentanyl deaths and incidences of addiction, but fentanyl has displayed anomalous behavior[4] and has been impacted by anomalous data compilation and analysis,[4-8] which have combined to impede progress. Thus, illicit fentanyl has become a “perfect storm” in science.

Results and Discussion

Anomalies have contributed to confusion, research delays, and thereby an increasing number of deaths. Using CDC reports [2], we determined death rates for years 1999 through 2022 due to fentanyl, as shown in Figure 1 below. The displayed surge in death rates starting

*Corresponding author: djnelson@ou.edu

in 2013 reveals how the fentanyl data caught the US scientists, politicians, and public off guard. The death numbers increase from less than 3000 in 2013 up to about 73,000 in 2022.

Furthermore, we disaggregated the CDC fentanyl deaths for years 2015 through 2021 by race and gender, as shown in Figure 2 below. These data reveal that black males constitute the demographic group which is most impacted by fentanyl.

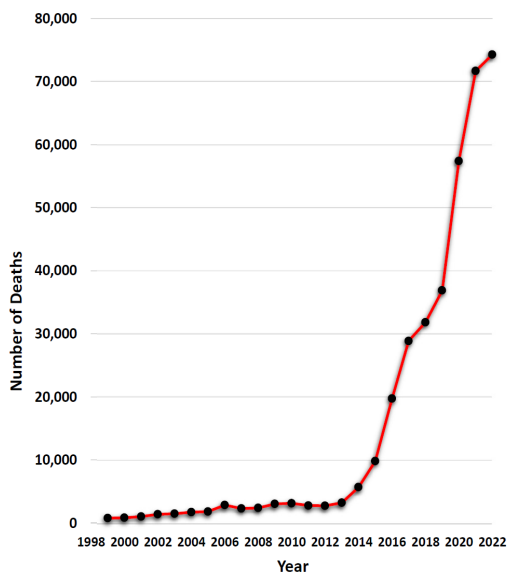


Figure 1. Number of deaths per year for years 1999 through 2022.

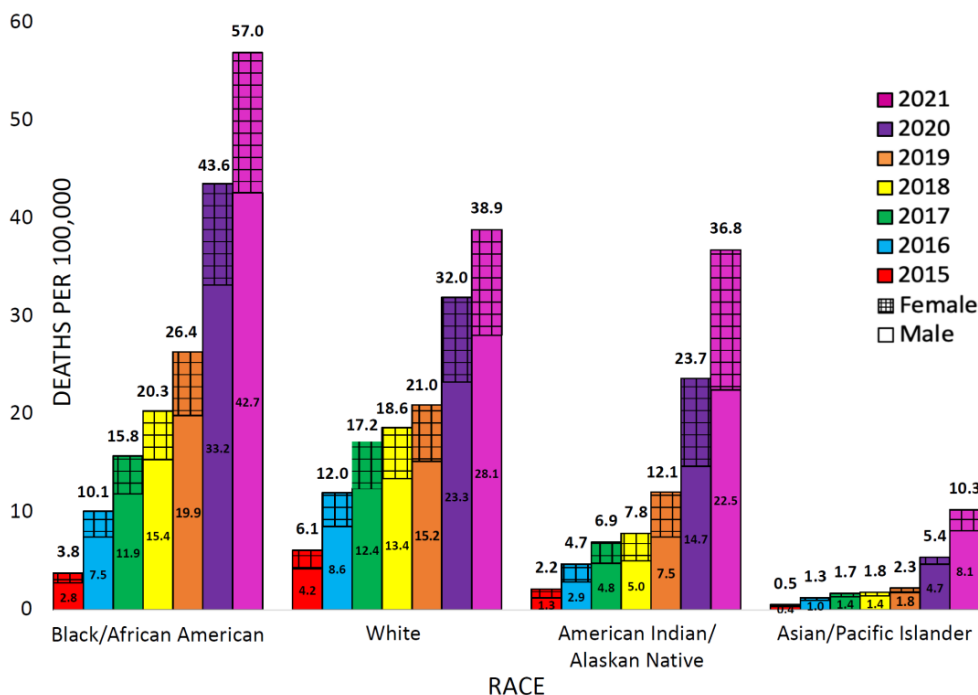


Figure 2. Fentanyl death rates for years 2015 through 2021, disaggregated by race and gender.

Accomplishing the work needed to reduce deaths will require talents from multiple scientific disciplines, and the corresponding scientists being inspired to make the effort. However, scientists appreciate order and are uncomfortable with confusion. Solid reliable research can't be built upon anomalies.

Fentanyl displays anomalous chemical behavior,[4] and some fentanyl data were handled in anomalous ways [4-8]. Anomalies in fentanyl data compilation and analysis were caused by researchers, so these can be clarified and resolved. Anomalies in fentanyl reactivity can't be eliminated, but we can recognize and understand them, so we must accommodate and work around the anomalies when possible. Some examples of anomalous chemical behaviors of fentanyl and poor data compilation and analysis are listed and categorized below. Both types of anomalies, in addition to social challenges faced by people taking illicit fentanyl, and involvement by forces from other countries have combined to create a wicked problem, multi-faceted, difficult

to analyze, and unattractive due to anomalies and sheer size – a perfect storm in science. Currently, research on fentanyl has many anomalies; some examples are listed below.

Anomalies in fentanyl chemical behavior

Some specific anomalous chemical behaviors of fentanyl: (a) Research literature gives many different ratios of fentanyl versus morphine relative potencies, with ratios ranging at least as widely as 0.6 to 165.[4] The potency ratios of fentanyl and morphine versus other fentalogs, also vary considerably, with wide-ranging relative potency values. (b) Several unexpected properties of fentanyl were reported recently, [4] such as (i) increased ability to interact within the active site due to its conformational flexibility, (ii) access to the active site through the lipophilic pathway, and (iii) reduced sensitivity to reversal by naloxone compared to other opioids.

Anomalies in data compilation and analysis

Uncertainty in fentanyl data can also be caused by inappropriate data compilation and analysis.

In some cases, data selected for inclusion in reports or review articles weren't obtained under similar reaction or collection conditions and could not give accurate comparisons.[4,6] For example, a very important international publication,[5] intended to inform researchers globally, tabulated and compared many relative potencies for fentanyl, morphine, and other fentalogs obtained by assorted research groups using different reaction conditions.[6,8] This unnecessarily introduced discrepancies, because potency values were available for almost all the fentalogs listed, having been originally determined by Janssen under identical conditions.[7]

Furthermore, these illogical comparisons among fentalog potencies were made, without considering (i) the ease of retrieving the cited data, (ii) the methodology for its generation, nor (iii) the information details sufficient to compare the data without obtaining the source document. Obtaining the original manuscript reporting these data is especially difficult in the following case.[5,6] Tracking the fentanyl:morphine ratio back through references [6] to the source [8] leads to a decades-old article, in an obscure journal, difficult to obtain, and written in Chinese, with no translation available. The methodology and reaction conditions had to be obtained by purchasing the article [8] through the National Library of Medicine and translating the text from Chinese. This revealed that the data were not obtained under identical conditions and are therefore not confidently comparable to the other data in the table.[5]

Moreover, it was not necessary to use data from this obscure article because data obtained under consistent conditions were readily available in Janssen's manuscripts.[7] Greater care for consistent methodology is warranted. Furthermore, unnecessarily using obscure data seems counter to the current goals for open access. More scientists may be attracted and inspired to research fentanyl and illicit fentanyl in the future, if its data are more consistent and easily available.

It is desirable to have accurate and comparable

potencies of fentalogs, with a common reference point, requiring that the potency determinations are carried out under the same conditions and methodology. This provides a knowledge base with a strong foundation.

Social influences and challenges to resolve; activities to build upon

Social aspects of illicit fentanyl must be considered also. Fentanyl is very high potency, so only a small amount laced into other street drugs is necessary to produce a dangerous high. If too much fentanyl is added to the street drug, or if the user takes too much, the user dies; each street drug user unwittingly plays Russian roulette. Thus, hundreds of people are poisoned in the U.S. each year. Solutions, clarifications, and consistency are urgently needed for illicit fentanyl, because stakes are high, and measured in terms of human lives. Time is also a factor, because the death rate is rising.[1,2]

One social challenge, which may be more symbolic than substantive is that fentanyl is frequently mispronounced as fentanol, especially by news people and those in government. [9] Some attempts to mitigate damages have been tried, but more are needed. For example, hanging fentanyl information posters for students in middle schools and high schools [10] didn't slow the increasing annual death rate. Recently another vaccine against effects of fentanyl was discovered, and more such research and development are necessary.[3] The SHIFT program [11] at The University of Texas at Austin draws on students to inform other students about the dangers of illicit fentanyl, in order to SHIFT the campus culture. All of these are helpful, but it seems that scientific research is not satisfying the public's thirst for progress on illicit fentanyl. Currently, the best approach to reach students seems to be peer-to-peer communication, such as is used in the SHIFT program.

Government influences and activities

Recent activities motivated the U.S. government to act regarding illicit fentanyl. For example, on Sep 14, 2022, eighteen U.S. State Attorneys General petitioned President Biden to declare it a Weapon of Mass Destruction.

[12] On Feb 15, 2023, there was a U.S. Senate hearing on illicit fentanyl coming into the U.S. from Mexico.[13] This confirmed that illegal fentanyl use in the U.S is encouraged and facilitated in part by some forces outside the U.S.; much illicit fentanyl comes from Mexico, where it is synthesized using precursors from China.[13] Recently, a congressional briefing made a case for declaring illicit fentanyl a weapon of mass destruction.[14]

Conclusions

This brief list of activities surrounding illicit fentanyl suggests a need for more research and more research support in this area. We must build a community, in order to work together widely on many fronts and track the status of fentanyl and its influences and consequences. Hopefully, the U.S. trend can be reversed from an annually increasing number of deaths caused by illegal fentanyl, to a declining number.

References

1. Families Against Fentanyl. *Fentanyl by the Numbers*. <https://www.familiesagainstoffentanyl.org/research/> (2022).
2. CDC - National Center for Health Statistics. *Drug Overdose Deaths 2021*. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm (2021).
3. A. Stone et al., Fentanyl conjugate vaccine by injected or mucosal delivery with dmLT or LTA1 adjuvants implicates IgA in protection from drug challenge. *npj Vaccines* **69**, 1-11 (2021).
4. E. Kelly et al., The anomalous pharmacology of fentanyl. *Br. Pharmacol.* **2021**, 1-16 (2021).
5. Recommended methods for the identification and analysis of fentanyl and its analogues in biological specimens. United Nations Office on Drugs and Crime. Page 19. United Nations, Vienna (2017).
6. I. Ujváry et al., Acryloylfentanyl, a recently emerged new psychoactive substance: a comprehensive review. *Forensic Toxicology*. **35**, 232–243 (2017).
7. W. Van Bever, C. Niemegeers, K. Schellekens, P. Janssen. *N*-4-substituted 1-(2-arylethyl)-4-piperidiny-*N*-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin. *Arzneimittel-Forschung*, **26**, 1548–51 (1976), and references therein.
8. Y. Zhu et al., Studies on potent analgesics. I. Synthesis and analgesic activity of derivatives of fentanyl. Yaoxue Xuebao [Acta Pharmaceutica Sinica] **16**, 199-210 (1981).
9. President Joseph R. Biden, State of the Union Address, Washington, DC. (Feb 7, 2023). <https://www.whitehouse.gov/state-of-the-union-2023/>
10. Personal communication. Dr. Cato T. Laurencin, University of Connecticut. (Nov 4, 2022).
11. SHIFT the Campus Culture. The SHIFT Office, The University of Texas at Austin. Austin, TX. Accessed Feb 15, 2023. <https://shift.utexas.edu/get-involved.html>
12. A. Moody et al., 18 States Urge President Biden to Declare Fentanyl a Weapon of Mass Destruction. (Sep 14, 2022). <https://www.scribd.com/document/594753242/9-15-Multistate-WMD-Letter-to-President-Biden#>
13. Foreign Relations Committee, Full Committee Hearing. Countering Illicit Fentanyl Trafficking. (February 15, 2023). <https://www.foreign.senate.gov/hearings/countering-illicit-fentanyl-trafficking>
14. Congressional Briefing, The Case for Classifying Illicit Fentanyl as a Weapon of Mass Destruction. (Feb 27, 2022). <https://drive.google.com/file/d/13TTe51EhhWBSfjGtviJb--ISsxNDq9k/view>

Submitted April 10, 2023 Accepted October 30, 2023