Expert Committee on Drug Dependence

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World Health Organization

Expert Peer Review for Tetrahydrofuranylfentanyl (THF-F)

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential: The critical review indicates that at the time of the report, there are no physical dependence studies available in laboratory animal or human studies involving tetrahydrofuranyl fentanyl (THF-F). The review speculates that dependence potential is "likely high" based upon the limited data that exists from adverse effects reports in humans as well as the observation that it is a μ-opioid receptor agonist.

Abuse potential: No controlled laboratory animal or human studies could be cited in the critical review. Data from controlled *in vitro* studies indicates it has affinity and efficacy as an agonist at the μ-opioid receptor which are consistent pharmacological effects observed with regulated opioid drugs.

b. Risks to individual and society because of misuse

Information specifically related to THF-F appears confined to reports from Sweden and the U.S. Sweden reported a total of 14 deaths with confirmed exposure to THF-F between 2016 and 2017. Other substances were apparently detected in these deaths. The STRIDA project reported an analytically confirmed THF-F intoxication in a male that suffered reduced consciousness, respiratory depression, and miotic pupils. The U.S. reported two confirmed fatalities associated with THF-F.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

The critical review indicates that THF-F has been seized as a liquid, in powder form, and as disk-shaped tablets. These reports appear to have mainly come from Sweden and the United States. Drug-user websites discuss and have sold THF-F. The peer reviewer could not find information related specifically to THF-F in sections "13. Non-medical use, abuse and dependence" or "14. Nature and magnitude of public health problems related to misuse, abuse and dependence". The frequently cited Zawilska (2017) review article in those sections never identifies data specifically associated with THF-F except in one instance in which it mentions that THF-F appeared on the Swedish drug market following the ban of acryloylfentanyl in 2016. Additional inference regarding the magnitude of the problem in countries has to be made from information cited in "6. Adverse reactions in humans" summarized in "1.b" above.

d. Need of the substance for medical (including veterinary) practice
The critical review indicates that there are currently no therapeutic applications or recorded medical uses for THF-F at this time. There also appear no marketing authorizations as a medicinal product for THF-F.

e. Need of the substance for other purposes (e.g. industrial)
Other than as an analytical reference compound, there is no industrial use for THF-F.

f. Measures taken by countries to curb misuse
The U.S., and at least seven European countries have THF-F controlled under drug control or medicines legislation. Note, the Annex was not available to the peer reviewer at the time of the review (10/4/17) to identify any new legislation.

g. Impact if this substance is scheduled
The impact if scheduled is likely minimal, except for the added bureaucratic expense by member states for adhering to the requirements of the Conventions.

2. Are there absent data that would be determinative for scheduling?

It would be helpful to have an expert opinion regarding the ease of convertibility into a scheduled compound. It would be also helpful to have controlled human and non-human dependence and abuse potential data available prior to a scheduling recommendation.

3. Other comments or opinions

In some cases, the peer reviewer was not sure what was actually known about THF-F versus what was likely to be the case based upon the pharmacology of other fentanyls. For instance, the first sentence of "6. Adverse Reactions in Humans" the critical report reads, "…the most serious acute health risk from using tetrahydrofuranylfentanyl is respiratory depression, …", is verbatim from the EMCDDA-Europol report on THF-F except the word "probably" was omitted from the EMCDDA-EUROPOL report. That is, the EMCDDA-Europol report reads, "….the most serious acute health risk from using tetrahydrofuranylfentanyl is *probably* respiratory depression, …" communicating the difference from what we *know* versus what we would *expect* of THF-F as a fentanyl. In other sections information is provided relevant to fentanyls but without documentation directly relevant to THF-F. For instance, in "13. Non-medical use, abuse and dependence" three total published references are provided in that section to characterize THF-F: 1) UNODC World Drug Report 2017; 2) Zawilska 2017; and 3) Helander and Backberg 2017. However, no specific reference to THF-F could be found in the UNODC 2017 or the

Helander and Backberg 2017 reports after searching for its mention. The single mention of THF-F in Zawilska 2017 was limited as described in 1.c above.

4. Expert reviewer's view on scheduling with rationale

To be considered under the 1961 UN Single Convention on Narcotic Drugs, THF-F needs to show a sufficiently similar abuse liability profile and the dependence-producing properties to drugs already controlled under that convention. Controlled in vitro studies indicates THF-F has affinity and efficacy as an agonist at the μ-opioid receptor which are consistent pharmacological effects observed with regulated opioid drugs such as morphine and fentanyl. An analytically confirmed THF-F intoxication indicate effects also consistent with regulated opioid drugs. Several deaths have been associated with THF-F use, although it is unclear whether it was the principal cause of death. Seizures of the drug have occurred, and it appears sold on the Internet. Thus, THF-F appears to comply with conditions to suggest inclusion in Schedule I of the 1961 Convention. Whether to also suggest inclusion of THF-F in Schedule IV of that Convention requires discussion. Although it is without substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV, the lack of available data does not automatically force concluding it is also particularly liable to abuse and to produce ill-effects to additionally recommend its inclusion in Schedule IV of the 1961 UN Single Convention on Narcotic Drugs.