Expert Committee on Drug Dependence

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World Health Organization

Expert Peer Review for 4-Fluoroamphetamine (4-FA)

1. Comments based on the review report

a. Evidence on dependence and abuse potential

Dependence potential:

There have been no additional studies since the previous WHO Review. The Critical Review Report describes self-administration studies that indicated 4-fluoroamphetamine (4-FA) functioned as a positive reinforcer under fixed-ratio (FR) 25 schedule (biphasic dose-response) and progressive-ratio (PR) conditions but at a lower level than *d*-amphetamine (hypothesized to be due to serotonin releasing effects of 4-FA). In conditioned place preference studies, 4-FA did not induce behaviour associated with drug dependence. Supporting human studies do not exist nor do published medical assessments of chronic users.

Abuse potential:

Aside from some discrete *in vitro* transporter studies, there have been no additional studies specifically relating to abuse potential since the previous WHO Review. The Critical Review Report describes drug discrimination animal studies in which 4-FA displayed an amphetamine-like discriminative stimulus and substituted for fenfluramine (but not serotonergic agents MMAI or MBDB). The Critical Review Report states there are no human studies regarding abuse potential. Nevertheless, the Critical Review Report demonstrates there is evidence of abuse of 4-FA by users seemingly for its psychomotor/entactogen stimulant effects but it was reported to be often present as an adulterant in amphetamine and "Ecstasy" products therefore it is unclear what proportion of users actively sought the drug. However, in one European country 4-FA has recently established itself as a drug of choice (powdered form, tablets and capsules) in a subpopulation of recreational drug users associated with clubs and music festivals. 4-FA is a derivative of amphetamine which is listed in Schedule II of the United Nations 1971 Convention on Psychotropic Substances Convention on Narcotic Drugs.

b. Risks to individual and society because of misuse

The Critical Review Report details 4-FA to have properties that are also encountered with cocaine and other amphetamine-like psychostimulants with the ability to increase extracellular levels of dopamine, noradrenaline and serotonin. The reported adverse effects of 4-FA in users have seemingly been as a result of these features with psychostimulant symptoms such as agitation, tremor, restlessness and tachycardia but with some cases reporting pronounced cardiovascular toxicity, severe headache and cerebral hemorrhage. A review of fatal and non-fatal case data (analytically confirmed cases where 4-FA was detected) showed that 4-FA featured in four fatalities but any causative link was unclear due to the presence of other drugs or lack of information. Eighty-eight non-fatal cases were listed in the Critical Review Report (with twenty-eight reported in 2017) but other drugs were involved in the majority of cases or no additional analytical toxicological information was available. Therefore whilst there was clinical evidence of adverse effects to the individual, the exact significance or contribution of 4-FA remains unclear.

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

The Critical Review Report highlights its detection (through drug seizures or biological fluid detection) primarily within Europe, since at least 2007. In this region, 4-FA has been found in products sold as "Ecstasy" (tablets) and amphetamine powder but also an adulterant present in other illicit controlled substances. However, 4-FA is also available in its own right, either from on-line or off-line retailers and is specifically sought after. Importantly, since the previous WHO Review, in the Netherlands it has been reported to have established itself as a substance of choice in a subpopulation of recreational substance users, especially those who might prefer using this substance in a social context. Nevertheless, 4-FA does not appear to be widely marketed as a "research chemical" via the Internet or otherwise and could be considered to be linked more to "Ecstasy"/amphetamine markets.

d. Need of the substance for medical (including veterinary) practice

4-FA has no medical or veterinary use.

e. Need of the substance for other purposes (e.g. industrial)

4-FA has no industrial or other use.

f. Measures taken by countries to curb misuse

At the time the Critical Review Report was controlled (through national legislation) in Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Slovakia, Slovenia, Sweden, Turkey and United Kingdom.

g. Impact if this substance is scheduled

No specific information but there are no known approved therapeutic applications for 4-FA and it is not listed on the WHO Model List of Essential Medicines.

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

More data regarding abuse and dependence potential may be beneficial but there is evidence of actual abuse in humans. In poly-drug use, especially with other psychostimulants, it is difficult to determine the specific role of an individual substance so data regarding cases involving only 4-FA would be useful.

3. Other comments or opinions

The Critical Review Report clearly shows there are many published methods and techniques to detect 4-FA, however as 4-FA does not often feature in routine analytical toxicology this may limit its detection or identification in biological fluid of users. Consequently, the prevalence of 4-FA could be higher if more laboratories included the drug in routine drug testing methodologies, nevertheless 4-FA may be indicated during common immunoassay screening for amphetamines employed in a variety of drug screening situations. The ability to distinguish between the 2-, 3- and 4-FA isomers is also a consideration.

One significant change in relation to the previous WHO Review, is that 4-FA has seemingly gained specific popularity in a sub-population within a single country. As the exact reason for this is not fully understood, this could happen in other countries.

4. Expert reviewer's view on scheduling with rationale

Amphetamines can only be subject to the 1971 Convention by virtue of a previous Party agreement. From the available evidence 4-FA has similar abuse and ill effects to amphetamine (a Schedule II substance) and could be considered to have the capacity to produce dependence. Whilst 4-FA has no current therapeutic use, the guidelines describe a weighting towards the public health risk and I would propose that 4-FA has a "liability to abuse that constitutes a substantial risk to public health" (but not especially serious risk due to the somewhat limited magnitude of known fatal and non-fatal cases). As such I would recommend that 4-FA be listed as a Schedule II substance of the United Nations 1971 Convention on Psychotropic Substances Convention on Narcotic Drugs.