1. Comments based on the review report

a. Evidence on dependence and abuse potential

The critical report indicates that there is no study data available on the dependence potential of APINACA.

Information about the abuse potential of APINACA in humans is also no available. The initial indication of evidence of abuse appeared in 2011 upon the identification of APINACA in products. The report sustains that due to the close pharmacological resemblance of APINACA to THC, abuse of APINACA is likely to occur.

b. Risks to individual and society because of misuse

The report points out that the common view is that APINACA, like other synthetic cannabinoid receptor agonists (SCRAs), is used as a substitute for cannabis. Adverse effects of SCRA intoxications are more intense than with cannabis, possibly because of their high activity and ease of overdosing. The critical review report emphasizes that there appears to be a wide variety of herbal products containing a variety and varying quantities of SCRA. In general, acute symptoms of SCRA intoxications include tachycardia, hypertension, nausea/vomiting, hypokalemia, agitation, hallucinations, somnolence, mydriasis, chest pain, myoclonia, seizures, and acute psychotic reactions. Symptoms usually disappear within a few hours. Most of the symptoms are similar to those after high-dose cannabis, except for agitation and seizures which are usually not seen after high doses of cannabis.

In the WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD a total of 66 Member States answered the questionnaire for APINACA (AKB-48). Of these, only 27 respondents (AFR 1, AMR 5, EUR 18, WPR 3) had information on this substance. Sixteen respondents confirmed that there was recreational/harmful use of AKB 48; common route of administration being oral in two, inhaling/sniffing in nine and oral injection, inhaling/sniffing in one response. Eight respondents stated this was obtained only via trafficking, one via clandestine manufacturing and four via trafficking and clandestine manufacturing. Seven respondents reported on the common formulations of AKB 48 available with 6 reporting powder, and one powder and liquid forms. Three respondents also mention that AKB 48 is often smoked and six that AKB 48 is often found in herbal mixtures. When asked if AKB 48 was used by any special populations
six responded only in the general population and one responded that it was used by the general population and in clubs. One emergency room visit due to AKB 48 was reported in 2013. Five respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by AKB 48. These included vomiting, hallucination, disorientation, anxiety, agitation, paranoia, panic attacks, concentration and coordination difficulty, xerostomia, seizures, elevated blood pressure, tachycardia and loss of consciousness. One respondent reported drug related crimes involving postal delivery of NPS.

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

The critical report emphasizes that APINACA has been seized as a pure substance and as a substance spiked on herbal products:

From January 2010 to April 2013, the National Forensic Laboratory Information System (NFLIS) identified 525 reports regarding APINACA from forensic laboratories. The review indicates that a DEA program, The System to Retrieve Information from Drug Evidence (STRIDE), identified 40 cases and 112 records involving APINACA between January 2009 and April 2013. Submissions to DEA laboratories from January 2012 through April 03, 2013 have documented over 150 distinct packaging examples containing mixtures of UR-144, XLR11 and/or AKB 48. In Japan, APINACA has been identified in currently sold designer drugs. To the EMCDDA, seizures containing APINACA have been reported from Romania, Italy, United Kingdom, Czech Republic, Latvia, Croatia, Denmark Spain, Belgium, Hungary, Germany, Sweden, and Bulgaria.

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

There is no therapeutic use indicated in the report. In the WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD there was no use stated for animal/veterinary care, but three respondents stated that this substance was used in medical and scientific research or as analytical standard.

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

The critical review reports no industrial use.

f. Measures taken by countries to curb misuse

According to the critical review report APINACA is a Schedule I controlled substance under the US Federal Controlled Substances Act. It is under national control in Denmark (2013), Germany (2013), Hungary (2012), Lithuania (2013), Latvia (2013), Slovakia (2013), and Japan (2012); and under temporary control in New Zealand (2012).
g. Impact if this substance if scheduled

In the WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD twenty-three respondents, out of twenty seven, reported that if AKB 48 was placed under international control, they would have the laboratory capacity to identify the substance.

2. Additional information to the critical review report

Gurney et al provides a thorough review on aspects related to Pharmacology, toxicology and adverse effects of synthetic cannabinoids drugs. They explain that the CB1 receptor is responsible for the psychotropic effects of cannabis, and therefore the ability of a ligand to bind to and act as an agonist at the CB1 receptor may indicate its potential as an alternative to marijuana for recreational use. On the other hand, CB2 receptors are largely viewed as immune modulators and as such are the target for potential therapeutic agents.

An additional aspect explained in this reference, also pertaining to preclinical data, is that even though binding affinity provides an important indicator for evaluating the abuse potential of a synthetic cannabinoid, it is also necessary to evaluate the efficacy and potency at the CB1 receptor. In this sense the article refers to a thorough review of in vitro and in vivo bioassays that have been used to evaluate the ability of compounds to elicit response by binding to the CB1 and/or CB2 receptors. These assays can be used to evaluate the structure-activity relationship (SAR) of synthetic cannabinoids. The effects of small changes in the molecular structure can thus be assessed and quantified. The authors explain that the majority of SAR studies have been performed on compounds with a high affinity for the CB2 receptor because the primary goal of many researchers was to identify compounds with therapeutic potential. They also clearly indicate that since the rise in popularity of synthetic cannabinoids for recreational use, more studies are being performed on compounds that bind preferentially to CB1. The most common approach used to determine if a specific analyte is an agonist for the CB1 receptor is to assess its binding affinity, evaluate guanosine 5′-O-[gamma-thio] triphosphate (GTPγS) binding as an indicator of signal transduction, and then to perform a panel known as the mouse tetrads assay to determine physiological effects in an animal model.

Gurney et al describe that cannabinoids have been reported as being useful in the treatment of pain, nausea, vomiting, epilepsy, ischemic stroke, cerebral trauma, multiple sclerosis, cancerous tumors, movement disorders such as Parkinson’s and Huntington’s disease, mood and anxiety disorders, and other disorders and diseases in humans and animals. In general, the toxic effects in humans appear to have the potential to be more severe and unusual than THC and include psychosis, seizures, tachycardia, autonomic hyperactivity, and suicidality. (Gurney SMR, Scott KS, Kacinko SL, Presley BC, Logan BK: Pharmacology, toxicology, and adverse effects of synthetic cannabinoid drugs; Forensic Sci Rev 26:53; 2014.)
3. Other comments or opinions

Gurney et al also specify that halogenation, especially fluorination, of the aliphatic side chain of established cannabinoid agonists is a popular approach to synthesizing novel active drugs and attempting to increase their potency. In their experience APINACA (AKB-48), and ADBPINACA are encountered in mixtures alongside their 5-fluoropentyl analogs.


4. Expert reviewer’s view on scheduling with rationale

Evidence presented is consistent with the characterization of synthetic cannabinoid receptor agonists (SCRAs) and as such it is used as a substitute for cannabis. There is information on dependence or abuse potential, although is not complete. Due to the resemblance of APINACA to THC, abuse of APINACA is likely to occur. There is information on its potential to induce harm effects in humans. Consequently it meets the criteria for inclusion in Schedule I of the 1961 Convention, but, on the other hand, its liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV. In view of this scheduling in Schedule IV could be considered.