

Title: Identification of Synthetic Cannabinoids Seized, Consumed and Associated with Deaths in Kuwait in 2018 using GC-MS and LC-MS-MS

Synthetic cannabinoids (SCBs) are a class of novel psychoactive substances (NPSs) that are being used for recreational purposes and many of these compounds are being further developed to overcome drug control laws. To be legally used, possessed, and distributed, SCBs packages are labeled with a disclaimer indicating that they are not for human consumption. Instead, SCBs are marketed as herbal incense and sold under variety of names including "Spice," "K2," "Cloud 9," "Mojo," and "Dreamer," among others. SCBs come in different forms, including dried leaves or resin, oily paste, incense, or powder. The powder is typically white; however, it can assume other colors and can be dissolved in ethanol or acetone and sprayed on dried leaves or plant material. The dried leaves are usually packaged with appealing designs, containing approximately 0.4-3.0 g of product sprayed with one or more types of SCBs and are consumed by smoking (using either pipes or cigarette papers), infusion, or inhalation.

The different types of SCBs for sale have substantial variability in their molecular structures; variations exist within the same product and even within the same package. Herbal mixes may contain multiple constituents other than SCBs, including preservatives, additives, fatty acids, esters, amides, benzodiazepine phenazepam, or *O*-desmethyltramadol, an active metabolite of the opioid medication tramadol. Moreover, SCBs have reportedly been combined with other drugs (i.e., a polysubstance), such as nicotine, alcohol, amphetamine, methamphetamine, tramadol, diphenhydramine, or cocaine.

SCBs are extremely potent, highly efficacious, and act as full agonists of cannabinoid receptors. According to the United Nations Office on Drugs and Crime, SCBs are classified according to their chemical structures because many SCBs were designed based on the chemical structure of THC, although some do not share any structural similarities with natural cannabinoids. SCBs that are structurally related to THC are referred to as 'classical cannabinoids', whereas SCBs that are structurally dissimilar to THC are referred to as 'non-classical cannabinoids'. A combination of the structural features of classical and non-classical cannabinoids can generate another group of SCBs referred to as hybrid cannabinoids. Aminoalkylindoles is another group that has been divided into subgroups, including cyclopropylindoles and indole carboxamides. Furthermore,

naphthoylpyrroles, naphthylmethylindenes, and eicosanoids are other groups in the family of SCBs.

Because SCBs possess high binding affinities to the cannabinoid receptors, 1-100 times more potent than THC, some SCBs can be more harmful than THC. For example, SCB intoxication produces a wide range of adverse physiological and psychiatric effects that vary in severity and duration. Some of these toxic effects include psychosis, respiratory depression, cardiac arrest, nephrotoxicity, hyperthermia, acute cerebral ischemia, and seizures. Moreover, other negative effects have been reported such as palpitation, paranoia, intense anxiety, nausea, vomiting, confusion, and poor coordination. According to the Centers for Disease Control and Prevention, there have been several deaths associated with the abuse of synthetic cannabinoids and the number of deaths is rising.

Although very harmful, SCBs are still considered the most popular NPSs. For example, SCBs were found to be the most used and diverse drug group in Europe during 2017, constituting 45% of all NPS, whereas synthetic cathinones (SC) and phenethylamines constituted 33% and 3%, respectively. Also, the Forensic Medicine Institute in Turkey reported that SCBs were the most common group found amongst the 1357 narcotic types confiscated by the police between 2016 and 2017. Many types of SCBs were detected in Turkey and some of them were also obtained in other countries, including Germany, Italy, Sweden, Taiwan, Korea, Japan, and the US.

Despite the increasing body of information regarding the use, diversity, and effects of SCBs worldwide, to our knowledge there is hardly any information regarding this subject in the Gulf countries, and more specifically, in Kuwait. This lack of information is not because people in these countries are not using these compounds, but rather because there is a lack of published data, possibly because some of these compounds have only been classified in Kuwait as Schedule II substances as of 2016. Thus, the purpose of our work is to identify and document the different types and classes of SCBs, the different SCB mixtures found within the same packs, and the other narcotics and/or psychotropics mixed with SCBs in Kuwait in 2018. This is performed by using the GC-MS for the seized samples and the LC-MS/MS for biological samples either from suspected abusers or deceased individuals. Moreover, our toxicology data will shed some light on the most commonly used SCBs in Kuwait and highlights the SCB-associated deaths that occurred in Kuwait during 2018.