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EDITORIAL

Semi-synthetic cannabinoids: An emerging challenge for clinical and regulatory toxicology

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One of the most fascinating aspects of contemporary clinical toxicology is undoubtedly the study of the epidemiology of poisonings. Unlike other medical specialties, in which the pace of discovery of new agents involved in the pathophysiology of diseases is relatively stable, the exponential emergence of new xenobiotics and their implications for human health has made toxicological science one of the most dynamic fields, with strong projected growth.

The market for new psychoactive substances (NPS) exemplifies this phenomenon. In recent years, consumption patterns have shifted, with previously known compounds such as nitrous oxide, ketamine, and mephedrone, which were used only sporadically, re-emerging alongside the introduction of entirely new synthetic molecules. Among the latter are semi-synthetic cannabinoids (SSCs), including hexahydrocannabinol (HHC) and tetrahydrocannabiphorol (THCP). These compounds are synthesized from cannabidiol (CBD), a cannabinoid abundant in *Cannabis sativa* and traditionally considered devoid of psychotropic effects. However, chemical modifications transform it into molecules with high psychotropic potential and unknown toxicological profiles.[1,2]

It is not possible to understand the emergence and perceived "success" of these products without considering the recent history of the rapidly expanding cannabis industry, in which CBD has been, and in many countries continues to be, the central driving force, largely owing to its status as a non-scheduled substance. The abundance of this "raw material" in commercial markets made it inevitable that surplus production would be redirected toward the development of other, more profitable substances.

The first reported case of an SSC identified by the European Union Drugs Agency (EUDA) occurred in 2022, when it was marketed as a "legal" alternative to cannabis. At present, these molecules have been reported in 27 countries of the European Union (EU). Based on the most recent EUDA report, in 2024 a total of 20 new cannabinoids were identified, 18 of which were SSCs, accounting for 40% of the new substances detected by the agency's early warning system that year. These compounds have been found in edibles (e.g., gummies), vaping devices, and in products marketed as CBD that were subsequently shown to be adulterated.[3]

Knowledge of the short and long term clinical toxicological effects of SSCs remains limited, given the

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relatively short period since their emergence. In addition, the lack of specific analytical standards in clinical and toxicological laboratories further hampers accurate assessment. Nevertheless, since 2024, cases of acute intoxication associated with the use of these cannabinoids have been reported.[4,5] The clinical presentation following oral exposure is characterized by initial nausea and vomiting, followed by alterations in the level of consciousness ranging from profound sedation to extreme agitation, depending on the case. This symptom profile closely resembles that observed in oral cannabis overdose,[6] raising concern about an unusually high pharmacodynamic potency at endocannabinoid receptors within the central nervous system.

In Spain, the exponential increase in acute intoxication cases requiring hospital care during 2024, and their subsequent reporting to public health agencies, were the crucial factors that led to the regulation of this molecular group under Order SND/380/2025 of April 14, 2025.[7] Beyond the legal restriction, however, the progressive technological sophistication and globalization of producers and distributors of these substances necessitate increasingly close collaboration among clinical toxicologists, public health authorities, and national and supranational regulatory agencies. Such coordination is essential to mitigate their impact on public health, alongside educational campaigns to inform the general population about the risks associated with their use.

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