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Short communication

Regulation on pesticide residues use and testing in cannabis and cannabis-based products in Europe and human exposure risk

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Pesticide use in cannabis cultivation

Pesticides prevent or kill most pests and diseases and increase the likelihood of successful harvest of cannabis. They are applied pre-plant, i.e. on soil prior to planting, at all stages of cultivation and on harvested (dried) plants to prevent mold. Unintended pesticide contamination of cannabis may occur by cross-contamination through wind, ventilation intakes, surface, well waters and/or recycled water. Later crops may also be contaminated by using long-term contaminated tools, lights and ventilation systems during their cultivation and harvesting (Canada & Health Canada, 2019). From plant material, pesticides migrate to extracts and concentrates and to final cannabis-based products, in levels depending upon the selected extraction/concentration methods. When used for recreational purposes (seldomly in medical), cannabis is smoked, vaped or dabbed using water/glass/paper pipes without filters and potentially high quantities of pesticide residues and their pyrolysis products formed as a result of high combustion temperatures (160-480°C) are inhaled. Presence of pesticide residues in oral medical cannabis products have to be paid special attention, since medical cannabis patients are more susceptible to the toxic effects due to immunological or hepatic illnesses (Raber et al., 2015).

Pesticides regulations in Europe

Neither pesticide use prohibition/allowance nor mandatory pesticide testing for medicinal cannabis derived products is established in **Austria** (*Narcotic Drug Act, 2016*, n.d.), **Croatia** (*Zakon o Suzbivanju Zlouporabe Droga.Pdf*, n.d.), **Cyprus** (*Law Amending Laws on Drugs and Substances Laws of 1977 to 2016*, n.d.), **Greece** (*Law 4523/2018*, n.d.), **Italy** (*Decreto Uso Medico Cannabis, 2015 .Pdf*, n.d.), **Lithuania**, for both medicinal cannabis and industrial hemp (*The Law on the Control of Drugs and Psychotropic Substances*, n.d.)**, Luxembourg** (Mutsch, n.d.)**, United Kingdom** (Criminal Justice Act. 2003), **Portugal** (*Lei No.8/2019*, n.d.)**, North Macedonia** (*Zakon Za Izmenuvanje i Dopolnuvanje Na Zakonot Za Opojni Drogi i Psihotropni Supstancii, 2016*, n.d.)**, Romania, Malta** (*Production of Cannabis for Medicinal and Research Purposes Act, 2018.Pdf*, n.d.), **Czech Republic** (*Sbirka Zakonu, 2013.Pdf*, n.d.), **Poland, Finland, Georgia** and **Germany**. Pesticide testing according to Ph. Eur 2.8.13 is mandatory only in **the Netherlands** for all cannabis flower and cannabis oil products (*Guidelines for Cultivating Cannabis for Medical Purposes*, n.d.). In **Switzerland, San Marino** and **Norway** one medical cannabis products with <1% THC is approved (Sativex®, and Bedrocan® in Norway), but no explicit provision for medical use exists within current law. **Denmark** and **Ireland** have ongoing pilot projects for medical cannabis use while it is still illegal (Aguilar et al., n.d.).

Human exposure to pesticide residues in cannabis cultivation and cannabis-based products

Consumer exposure to pesticide residues may occur during ingestion of cannabis products, edibles or recreational inhalation of cannabis (smoking, vapourizing, dabbing, i.e vapourization of concentrated butane hash oil),

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causing low-dose chronic toxicity. Inhalation is the most potent route of exposure, as it overpasses first-pass metabolism and results in high systematic bioavailability of pesticide residues and their pyrrolitic degradation products generated by heating and combustion (Sullivan et al., 2013), such as hydrogen cyanide from myclobutanil combustion, causing neurological, respiratory, cardiovascular and thyroid problems (Dryburgh et al., 2018). Inhalation exposure strongly depends on stability, volatility and degradation of pesticide residues during heating and combustion, individual user behaviours: use of particulate matter filter, breath depth, length of inhalation hold time and choice of heating method. To date, only one study confirms presence of >60% of initial cannabis pesticide content in cannabis smoke (Sullivan et al., 2013) and no study addresses neither exposure levels during vaporizing and dabbing nor pharmacokinetics and toxicity profiles of pesticide residues (Dryburgh et al., 2018). Oral administration of medical cannabis and cannabis edibles is the most common and only route with established tolerances and MRLs. Systemic bioavailability of pesticide residues is lower due to first-pass metabolism, which may indicate hepatic toxicity and formation of less/more toxic metabolites.

Interventional staff working at indoor cannabis plantations is at high risk of acute pesticide toxicity, as it is exposed to pesticide residues from plantation atmosphere, while in touch with irrigation water contaminated unintendedly during plant spraying or during application of solid pesticide formulation that generate dust while being loaded into the application equipment (Damalas & Eleftherohorinos, 2011; Stone, 2014). Despite their low volatility, pesticides are found in carbon filter of indoor cannabis cultivations (Cuypers et al., 2017), supporting high probability of inhalation exposure.

Dermal exposures are also significant, as they depend upon the exposed body part, amount and duration of exposure and pesticide formulation (Kim et al., 2017). They can occur directly, through accidental spills and leakages, faulty spraying equipment, mixing and loading, misapplications and during re-entry into treated areas or indirectly,.through clothing contamination or hand-to-mouth transfer during harvesting and processing (Damalas & Eleftherohorinos, 2011; Stone, 2014). Eye adsorption is important only for granular pesticides (Kim et al., 2017).

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