by Claire Kruger and Robert Lodder

Establishing Limits for **THC Content in Hemp-Derived Foods**

Many foods are now being formulated to include oils and seeds from the hemp plant because of the favorable nutrient profile of these sources. Hempseeds, like most seeds, are a source of unsaturated fatty acids, including essential fatty acids as well as other nutrients, such as vitamins, minerals, fiber, and protein (Callaway et al. 2004). Marijuana and hemp come from the same species of plant, *Cannabis sativa*, but from different varieties or cultivars. Hemp, also called "industrial hemp," refers to cannabis varieties that are primarily grown as an agricultural crop and is characterized by plants that are low in Δ9-THC (Δ 9-tetrahydro-cannabinol, marijuana's primary psychoactive chemical). Hemp is cultivated from cannabis stalks and seeds, which contain only trace amounts of the psychoactive cannabinoid Δ9-THC (Johnson 2013). By contrast, marijuana is composed of cannabis flowers, or buds, which contain 3%–15% of Δ9-THC by weight, an amount that has increased over the past decade. The seed contains less than 0.5 ppm Δ9-THC and is wrapped in specialized leaves called the calyx that do produce Δ9-THC and may cause some contamination of the outside of the seed coat (ANZFA 2002, FSANZ 2012).

Sen. Mitch McConnell, R-Ky., recently introduced a bill (Hemp Farming Act 2018) that would allow states and tribes to regulate hemp production. As written, "hemp" would be defined as follows: the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a THC concentration of not more than 0.3% (3,000 ppm or 3,000 mg/kg) on a dry weight basis. In the United States, there is no standard analytical or health-based method to define quantity of Δ9-THC as nondetectable or safe. To put the proposed THC limit in perspective, a 60 kg person consuming 10 g of a hemp product containing 0.3% THC would ingest 30,000 µg THC.

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It is critical, therefore, to examine the available scientific data to define a level of THC contamination in a hemp food product that presents an acceptable lack of health risk for consumers. Although many clinical studies on THC are available, the vast majority have been designed to gain insight into the physiological effects of THC and establishing effective doses in ameliorating various symptoms associated with disease states, rather than determining the threshold for the effects under investigation. In addition, most studies have investigated the effects of smoked cannabis and compared the physiological and psychological measures with the mg of THC consumed, rather than establishing the bioavailability (blood or tissue levels) and metabolic fate of the THC at the time the measures were performed. Importantly, there is a paucity of studies where THC was orally administered.

The issue of limits for THC was tackled in 2011 by the European Food Safety Authority (EFSA) Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). They conducted a risk assessment on the safety of hemp for use as animal feed and based on application of a 100-fold safety factor to the Lowest Observed Effect Level (LOEL) of 40 µg THC/kg bw, derived from clinical studies reporting psychotropic effects, derived a provisional maximum tolerable daily intake (PMTDI) of 0.4 µg/kg bw (corresponding to 24 µg THC for a 60 kg adult) (EFSA 2011).

In 2012 the Food Standards Agency of Australia New Zealand (FSANZ) conducted a risk assessment for THC and established a Tolerable Daily Intake (TDI) of 6 µg THC/kg bw or 360 µg for a 60 kg person (FSANZ Support Document 1 2012). FSANZ concluded that following oral administration, the most sensitive adverse effects observed in humans appear to be related to skill performance (e.g., hand-eye coordination and reaction time) and cognitive tasks (e.g., performance on arithmetic tasks). The TDI was derived from the results of a human study in which the effect of oral THC on skill performance, cognitive function, and mood was examined, and on a self-reporting intoxication scale, the lowest dose level was not distinguishable from placebo, although there was a dose-related effect reported at the other dose levels (Chesher et al. 1990).

Regulatory review of health endpoints for THC exposure have relied on psychotropic effects from clinical studies to derive a No Observed Adverse Effect Level (NOAEL) for exposure; however, study designs and outcomes measured to assess these endpoints vary considerably. Subjective measures such as appetite or nausea improvement, self-reported intoxication, mood rating scales, and visual analog scores have been utilized.

The safety factor approach applied to a NOAEL from a single clinical study suffers from major limitations that have been described in the literature, including strict dependence on dose selection, dose spacing, and sample size of the study from which the critical effect has been pinpointed. In addition, the safety factor approach does not take into account the shape of the dose–response curve.

The bootstrap method is a resampling technique used to estimate statistics on a population by sampling a data set with replacement (Lodder and Hiefje 1988). The bootstrap simulation methodology, based on a set of studies, may be a better approach to utilizing data from numerous clinical studies with varying study designs and endpoints than the approach taken by authoritative and regulatory bodies that utilized data from a single study. The bootstrap distribution of NOAELs and observed effects can be generated from a relatively small sampling of publications, and from this distribution an estimate of the actual NOAEL and observed effects can be made. For the bootstrap method implementation, defining an appropriate subset of studies with appropriately robust methodology that utilize objective measurement of reliable and sensitive physiological endpoints is critical.

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One criterion for selection is the use of objective and/or sensitive measures of response that are correlated with blood levels to provide additional confirmation of the administered dose. Studies that report blood levels of THC can be selected for the bootstrap method, as these are potentially better controlled in terms of compliance with dosage administration and thus potentially more useful in establishing dose-response. Heart rate is a very robust and sensitive parameter, which is affected by THC at the lowest doses (Klumpers et al. 2011). The fact that vital signs are objective, quantifiable, routinely measured, and highly standardized endpoints reported in most clinical studies, makes heart rate a highly suitable endpoint for the bootstrap analysis. Objective CNS measures of THC effects on psychomotor and cognitive performance are more likely to be standardized than are patient surveys. These measures include tests that measure reaction time, body sway, eye-hand coordination, standing steadiness, and are more quantifiable than Visual Analog Scale effects of drug intoxication. Measures of mental performance that can be assessed include endpoints such as task recall, verbal learning, visual information processing, and reasoning tasks.

From a bootstrap analysis of an appropriate subset of clinical studies that investigated objective endpoints of heart rate, blood pressure, or psychotropic effects, a TDI of 1.5 µg/kg/day or 90 µg/day for a 60 kg person may be derived utilizing identified NOAELs with application of safety factors to account for limitations of the data set and extrapolation to lifetime exposure.

Defining the most sensitive endpoint to establish a NOAEL and deriving a health-based threshold for response can be challenging for a contaminant such as THC. The bootstrap method may be a valuable tool to provide health-based limits that protect human well-being. **FT**

References cited are available via hyperlinks in the digital version of this column.

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