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Standard Guide for Determining a Point of Departure (POD) or Assigning a Threshold of Toxicological Concern (TTC), if needed, for Use in a Toxicological Risk Assessment of a Non- Cannabinoid Ingredient Intended for Use in Cannabinoid Products for Vaporization¹

This standard is issued under the fixed designation D8587; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ϵ) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide is not meant to classify the non-cannabinoid ingredient or final product as safe for inhalation. Inhaling anything other than clean air poses an inherent human health risk.

1.2 This guide shall cover all formulated (manufactured) cannabinoid-containing products intended for vaporization regardless of the method of obtention (source) of the cannabinoids used in the product.

1.3 This guide shall cover all formulated (manufactured) cannabinoid-containing products intended for vaporization regardless of whether the cannabinoids can be classified as intoxicating.

1.4 This guide shall cover all formulated (manufactured) cannabinoid-containing products intended for vaporization regardless of the regulatory classification of the consumer product.

1.5 This guide shall cover all non-cannabinoid ingredients, regardless of the method of obtention (source), used in formulated (manufactured) cannabinoid-containing products intended for vaporization.

1.5.1 Because naturally-derived and synthetic compounds produce comparable biological effects, so long as their chemical structure and spatial orientation are identical, the method of obtention (source) of the compound is irrelevant to the need to conduct a toxicological risk assessment of the non-cannabinoid ingredients.

1.6 This guide includes considerations for thermal breakdown products of the non-cannabinoid ingredient through the process of aerosolization via vaporization device usage.

1.7 This guide excludes formulated (manufactured) cannabinoid-containing products intended for combustion as well as dry herbal materials and inhalers (for example, dry powder and metered-dose).

1.8 This guide excludes the cannabinoids themselves.

1.8.1 Exclusion does not mean risk assessment of cannabinoids is unnecessary or that they are risk-free, only that they are beyond the scope of this standard. Investigation into these areas is encouraged to expand knowledge and safety of cannabinoid-containing products.

1.9 This guide excludes impurities and contaminants within the non-cannabinoid ingredients that are otherwise regulated. It is the responsibility of the user of this standard to know the impurities and contaminants and action limits set by the AHJ.

1.10 This guide excludes interactions between the compounds in the cannabinoid-containing product intended for vaporization. Interaction may include chemical interactions between two or more substances that might form new substances. Interactions may also include biological interactions such as a terpene altering cannabinoid binding to a receptor or other types of pharmacokinetic or pharmacodynamic or toxicokinetic or toxicodynamic interactions.

1.10.1 Exclusion does not mean risk assessment of interactions between compounds in the cannabinoid-containing product intended for vaporization are unnecessary or that they are risk-free, only that they are beyond the scope of this standard. Investigation into these areas is encouraged to expand knowledge and safety of cannabinoid-containing products.

1.11 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.12 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the*

¹ This guide is under the jurisdiction of ASTM Committee D37 on Cannabis and is the direct responsibility of Subcommittee D37.08 on Personal/Household-Use Cannabis Devices and Appliances.

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Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.

2. Referenced Documents

2.1 *ASTM Standards*:²

D8270 Terminology Relating to Cannabis

2.2 *ISO Standards*:³

ISO 10993-17:2009 Biological Evaluation of Medical Devices - Part 17: Establishment of Allowable Limits for Leachable Substances

ISO 10993-18:2020 Biological Evaluation of Medical Devices - Part 18: Chemical Characterization of Medical Device Materials within a Risk Management Process

3. Terminology

3.1 *Definitions*:

3.1.1 *Related to Cannabis*—Definitions are in accordance with Terminology **D8270**, unless otherwise indicated.

3.2 *Definitions of Terms Specific to This Standard*:

3.2.1 *adverse effect, n*—alteration of morphology, functional capacity, growth, development or lifespan of the target organism under defined conditions of exposure which is judged to be adverse.

3.2.2 *analytical evaluation threshold, n*—the threshold at or above which the chemical analyst should identify and quantify a thermal breakdown product for toxicological assessment.

3.2.3 *clastogenicity, n*—a substance that causes DNA strand breakages or rearrangements that cause disruption of entire chromosomal sections.

3.2.4 *concentration, n*—the level of a substance of interest in a medium.

3.2.4.1 *Discussion*—Units may be expressed as %w/w, mg/L, mg/g, or mg/m³ of a medium, where the medium could include, but is not limited to, air, cell culture media, solvent, extract, or otherwise.

3.2.5 *contaminant (contaminants), n*—in reference to **1.9**, components not occurring naturally in cannabinoid extracts or non-cannabinoid ingredients deemed problematic by an AHJ which may have been introduced during the growing, processing or manufacturing procedures.

3.2.5.1 *Discussion*—Contaminants regulated by AHJs will vary from jurisdiction to jurisdiction. It is the responsibility of the user of this standard to know which contaminants are regulated in the jurisdiction in which the final product is intended to be sold.

3.2.6 *correction factor, n*—in reference to this guide, have units and are added to convert POD values from one unit of measure to another and adjust non-continuous rates of change to continuous rates of change.

3.2.7 *endpoint, n*—the biological or chemical response or effect assessed by a test method.

3.2.8 *exposure, n*—the total amount of a toxicant or other chemical taken in by the consumer or the test species in a toxicological study.

3.2.8.1 *Discussion*—Units may be in mg/day or mg/kg body weight per day.

3.2.8.2 *Discussion*—May also be referred to as “dose”.

3.2.9 *genotoxicity, n*—an adverse effect on the genetic material (DNA) of living cells that, on the replication of the cells, is expressed as a mutagenic or a carcinogenic event.

3.2.10 *good laboratory practice, n*—a set of principles to assure quality and integrity of non-clinical studies laid out in 21 CFR 58 and 2004/10/EC.

3.2.11 *generally recognized as safe (GRAS), adj*—a United States Food and Drug Administration designation that a chemical or substance added to food is considered safe by experts under the conditions of its intended use.

3.2.11.1 *Discussion*—GRAS status alone cannot demonstrate safety for non-cannabinoid ingredients used in cannabinoid-containing products intended for vaporization; however, the underlying data to determine GRAS status may be useful in the risk assessment.

3.2.12 *impurity (impurities), n*—in reference to **1.9**, components occurring naturally in the cannabinoid extracts or non-cannabinoid ingredients from the starting material or resulting from chemical interactions.

3.2.12.1 *Discussion*—Impurities regulated by AHJs will vary from jurisdiction to jurisdiction. It is the responsibility of the user of this standard to know which impurities are regulated in the jurisdiction in which the final product is intended to be sold.

3.2.12.2 *Discussion*—Impurities resulting from chemical interactions can include those resulting from the combining of cannabinoids with non-cannabinoid ingredients.

3.2.13 *in chemico, adv*—experiments which do not use any human or animal cells, but simply evaluate how a chemical interacts/reacts with certain materials.

3.2.14 *in silico, adv*—tests performed on computer or via computer simulation.

3.2.15 *in vitro, adv*—tests conducted outside of the body of the organism.

3.2.15.1 *Discussion*—These tests would include cultured cells.

3.2.16 *in vivo, adv*—tests carried out on the intact organism, although the evaluation of the toxic endpoint almost always requires pathological or biochemical examination of the test organism's tissues.

3.2.17 *lethal concentration, n*—the amount of a substance in air that when inhaled is expected to kill 50 % of a test sample when administered as a single exposure.

3.2.17.1 *Discussion*—Units may be expressed as mg/m³ or ppm.

3.2.18 *lethal dose, n*—the amount of an ingested substance that is expected to kill 50 % of a test sample when administered as a single exposure.

² For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at www.astm.org/contact. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

³ Available from International Organization for Standardization (ISO), ISO Central Secretariat, Chemin de Blandinnet 8, CP 401, 1214 Vernier, Geneva, Switzerland, <https://www.iso.org>.

3.2.18.1 *Discussion*—Units may be expressed as mg/kg.

3.2.19 *lowest observed adverse effect level, n*—the dose at which an adverse biological response is first observed.

3.2.20 *manufacturer(s), n—in reference to this guide*, is used to refer to both cannabinoid product and non-cannabinoid ingredient manufacturers.

3.2.21 *mutagenicity, n*—the production of genetic alterations by exposure to chemicals or radiation.

3.2.22 *new approach methodologies, n*—are approaches used in risk assessment to fill information gaps that aim to reduce animal use.

3.2.22.1 *Discussion*—Generally includes *in vitro*, *in chemico*, and *in silico*.

3.2.23 *no observed adverse effect concentration, n*—the highest exposure level of a chemical that, in a given toxicity test, causes no observable adverse effect in the test animals.

3.2.23.1 *Discussion*—NOAECs are typically reported in an inhalation study.

3.2.23.2 *Discussion*—Units may be expressed as mg/m³ or ppm.

3.2.23.3 *Discussion*—May also be referred to as the No Observed Effect Concentration.

3.2.24 *no observed adverse effect level, n*—the highest exposure level of a chemical that, in a given toxicity test, causes no observable adverse effect in the test animals.

3.2.24.1 *Discussion*—Units may be expressed as mg/kg.

3.2.24.2 *Discussion*—May also be referred to as the No Observed Effect Level.

3.2.24.3 *Discussion*—Free-standing NOAEL is the highest exposure tested in a study and no adverse effects were observed in the study. In this case, there may be higher exposures that do not cause adverse effects, but they were not tested for.

3.2.25 *non-cannabinoid ingredient, n*—any substance, excluding cannabinoids that is added in the formulation.

3.2.26 *point of departure, n*—the exposure chosen as a basis for making extrapolations needed for assessing risk.

3.2.26.1 *Discussion*—Commonly a NOAEL or LOAEL.

3.2.27 *reprotoxin, n*—a substance that can damage the reproductive process by increasing the incidence of non-heritable adverse effects in the offspring or impairing male or female reproductive functions, or both.

3.2.28 *short-term exposure limit, n*—the time-weighted average concentration of a substance over a 15 min period assessed not to be injurious to health.

3.2.29 *thermal degradation products, n*—the transformation of a material resulting from heat application leading to new chemical entities.

3.2.29.1 *Discussion*—May also be referred to as “thermal breakdown” products.

3.2.30 *threshold of toxicological concern, n*—an approach that relies on setting a level of human intake or exposure that is considered to be of negligible risk in situations of incomplete relevant chemical-specific toxicity data.

3.2.31 *time weighted average, n*—concentration of a substance over a period of time concluded not to be injurious to health.

3.2.32 *toxicodynamics, n*—the process of interaction of chemical substances with target sites and the subsequent reactions.

3.2.33 *toxicokinetics, n*—the disposition of substances in the body, including absorption, distribution, metabolism, and elimination.

3.2.34 *uncertainty factor, n—in reference to this guide*, are unitless values used to divide a POD to extrapolate between exposure conditions and account for uncertainties when deriving exposure limits.

3.2.34.1 *Discussion*—May also be referred to as “safety factors.”

3.2.35 *weigh, v*—when reviewing data, the process of analyzing and ranking data based on applicability and quality.

3.2.35.1 *Discussion*—The process of weighing will culminate in ranking the data as best, better, worse, etc.

3.3 Acronyms:

3.3.1 *AET*—Analytical Evaluation Threshold

3.3.2 *AHJ*—Authority Having Jurisdiction

3.3.3 *CAS*—Chemical Abstracts Service

3.3.4 *CF*—Correction Factor

3.3.5 *EFSA*—The European Food Safety Authority

3.3.6 *FEMA*—Flavor Extract Manufacturers Association

3.3.7 *GCP*—Good Clinical Practice

3.3.8 *GLP*—Good Laboratory Practices

3.3.9 *GRAS*—Generally Recognized As Safe

3.3.10 *LC50*—Lethal Concentration

3.3.11 *LD50*—Lethal Dose

3.3.12 *LOAEL*—Lowest Observed Adverse Effect Level

3.3.13 *JECFA*—Joint FAO/WHO Expert Committee on Food Additives

3.3.14 *NOAEC*—No Observed Adverse Effect Concentration

3.3.15 *NOAEL*—No Observed Adverse Effect Level

3.3.16 *OECD*—Organization for Economic Co-operation and Development

3.3.17 *POD*—Point of Departure

3.3.18 *RIFM*—Research Institute of Fragrance Materials

3.3.19 *STEL*—Short-Term Exposure Limit

3.3.20 *TTC*—Threshold of Toxicological Concern

3.3.21 *TWA*—Time Weighted Average

3.3.22 *UF*—Uncertainty Factor

4. Significance and Use

4.1 Significance:

4.1.1 This guide establishes an approach for conducting a toxicological risk-based assessment of non-cannabinoid ingredients designed to reduce the potential health risks when used in cannabinoid products intended for vaporization.

