



Designation: D8588 – 24

Standard Practice for Approach to Calculating the Daily Inhalation Exposure Limit for a Non-cannabinoid Ingredient Intended for use in Cannabinoid Products for Vaporization¹

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1. Scope

1.1 This practice 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 practice shall outline the steps for calculating the acceptable daily inhalation limit from a point of departure (POD) for a non-cannabinoid ingredient intended for use in a cannabinoid product for vaporization.

NOTE 1—To use this practice, the user must have previously determined the POD for the non-cannabinoid ingredient under investigation and six uncertainty factors stated in this standard and correction factors.

1.3 This practice shall outline the steps for identifying the maximum allowable concentration limit of a non-cannabinoid ingredient that could be used in a proposed formulation from a POD or a defined TTC.

1.4 This practice shall outline the steps for comparing the concentration of a non-cannabinoid ingredient in an existing formulation to the calculated acceptable daily inhalation limit from a POD or a defined TTC of the non-cannabinoid ingredient under investigation.

1.5 This practice shall provide example scenarios to aid in the usage of the practice and understanding of how to perform the calculation.

1.6 This practice shall not define the means for calculating the acceptable daily inhalation limit from data generated *in vitro*.

1.7 This practice shall not define the means for calculating the acceptable daily inhalation limit from a lethal dose (for example, LC50 or LD50).

1.8 This practice shall not define the means for determining a POD or TTC for the non-cannabinoid ingredient under investigation.

¹ This practice 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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1.8.1 A user must complete a toxicological risk based assessment to determine a POD or TTC for a non-cannabinoid ingredient under investigation. It is recommended to consult an experienced toxicologist when conducting the risk assessment.

1.9 *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.*

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

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 *acceptable daily inhalation limit, mg/day, n*—in reference to this practice, is (1) the result of a calculation using a POD, or (2) a selected TTC.

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

3.2.2.1 *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.

3.2.3 *corection factor, n*—in acceptable daily inhalation limit calculations, have units and are added to convert POD

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.

values from one unit of measure to another and adjust non-continuous rates of change to continuous rates of change.

3.2.4 *daily consumption rate, mg/day, n—in reference to this practice*, is the mass of cannabinoid containing product intended for vaporization that is inhaled by a consumer in one 24-hour period.

3.2.5 *daily inhalation exposure limit, mg/day, n—in reference to this practice*, is the value calculated by dividing the product of the concentration of the non-cannabinoid ingredient in the formulation and an expected daily consumption rate by 1000 mg/g.

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

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

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

3.2.7 *gavage, n*—a type of oral administration by means of a tube leading down the throat to the stomach.

3.2.8 *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.

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

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

3.2.10 *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.

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

3.2.11 *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.

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

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

3.2.13 *manufacturer(s), n—in reference to this practice*, is used to refer to both cannabinoid product and non-cannabinoid ingredient producers.

3.2.14 *maximum allowable concentration, %w/w, n—in reference to this practice*, is the value calculated by dividing the acceptable daily inhalation limit by an expected daily consumption rate.

3.2.15 *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.

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

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

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

3.2.16 *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.

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

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

3.2.16.3 *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.

3.2.17 *non-cannabinoid ingredient, n*—any substance, excluding cannabinoids, that is added to a formulation.

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

3.2.18.1 *Discussion*—Commonly a NOAEL or LOAEL.

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

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

3.2.20 *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.

3.2.21 *uncertainty factor, n—in acceptable daily inhalation limit calculations*, are unitless values used to divide a POD to extrapolate between exposure conditions and account for uncertainties when deriving exposure limits.

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

3.3 *Acronyms:*

3.3.1 *BW*—Body Weight

3.3.2 *CF*—Correction Factor

3.3.3 *EQ*—Equation

3.3.4 *GLP*—Good Laboratory Practices

3.3.5 *LOAEL*—Lowest Observed Adverse Effect Level

3.3.6 *NOAEC*—No Observed Adverse Effect Concentration

3.3.7 *NOAEL*—No Observed Adverse Effect Level

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

3.3.9 *POD*—Point of Departure

3.3.10 *TTC*—Threshold of Toxicological Concern

3.3.11 *TWA*—Time Weighted Average

3.3.12 *UF*—Uncertainty Factor

4. Significance and Use

4.1 *Significance:*

4.1.1 This practice provides a means of extrapolating non-cannabinoid ingredient consumption limits from various sources of data to human inhalation consumption limits.

4.1.2 This practice provides an easy to understand equation for calculating the acceptable daily intake (ADI) from a

non-cannabinoid ingredient under investigation, and breaks down the variables necessary to perform the calculations and their purpose.

4.1.3 When this practice is applied to product manufacturing it can improve consumer confidence in cannabinoid products and non-cannabinoid ingredients intended for vaporization.

4.1.4 This practice can aid manufacturers in reducing the potential health risks associated with their products while maintaining consumer access to a wide variety of cannabinoid-containing vaporization products.

4.1.5 This practice, when combined with an appropriate risk assessment, will help to direct regulators and manufacturers in prioritizing non-cannabinoid ingredients used in consumer products containing cannabinoids intended for vaporization for additional evaluation to reduce consumer health risks by focusing their efforts and limited resources on substances more likely to pose a toxicological risk.

4.2 Use:

4.2.1 This practice is **ONLY** intended to be used to reduce potential negative consumer health risks from vaping non-cannabinoid ingredients.

4.2.2 This practice is **NOT** to be used to identify a non-cannabinoid ingredient or cannabinoid product as being safe for inhalation. Following this practice does not give the authority to claim a non-cannabinoid ingredient or cannabinoid product is safe for inhalation.

4.2.3 This practice is intended to be conducted in consultation with an experienced toxicologist.

4.2.4 This practice is not intended to be used for calculating the acceptable daily inhalation limit from a lethal dose (for example, LC50 or LD50), or from data generated *in vitro*.

4.2.5 This practice can be used to reduce consumer health risks based on information available today for non-cannabinoid ingredients used in cannabinoid products intended for vaporization.

4.2.6 This practice can be used to calculate the most conservative acceptable daily inhalation limit for a non-cannabinoid ingredient under investigation.

4.2.7 Regulators can use this practice in combination with an appropriate risk assessment for deriving individual ingredient limits. Using this practice, state regulators will have a scientific tool to create restrictions that can provide protection to consumers and encourage legal cannabinoid-containing product manufacturers and consumers to stay in the regulated market.

4.2.8 It is the responsibility of the user to understand the concepts presented in this document and to utilize them appropriately.

5. General Procedure

5.1 If evaluating a non-cannabinoid ingredient that is **NOT** currently utilized in a cannabinoid product for vaporization, use the procedure outlined in Section 6 to determine the acceptable daily inhalation limit and the maximum concentration limit for that non-cannabinoid ingredient in a cannabinoid product for vaporization.

5.2 If evaluating how the amount of a non-cannabinoid ingredient currently being utilized in a cannabinoid product for vaporization compares to the acceptable daily inhalation limit for that non-cannabinoid ingredient, use the procedure outlined in Section 7.

6. Procedure 1 – New Product Formulation

6.1 Conduct a risk-based assessment on the non-cannabinoid ingredient of interest to determine the point of departure (POD).

6.1.1 If no data is available, or if available data lacks robustness to confidently choose a POD, the threshold of toxicological concern (TTC) may be an acceptable alternative. If a TTC value is intended to be used, proceed to 6.4.3.2.

6.1.2 It is highly recommended to have a toxicologist perform or review the risk-based assessment.

6.2 Determine the uncertainty factors (UFs) necessary to extrapolate between exposure scenarios and account for uncertainty when deriving exposure limits.

6.2.1 UF categories include:

6.2.1.1 Extrapolating from animal studies to humans (inter-species);

6.2.1.2 Differential sensitivity among the human population (intraspecies);

6.2.1.3 Extrapolating from shorter duration studies to lifetime exposure;

6.2.1.4 Extrapolation from oral exposure to inhalation route to account for (1) toxicokinetic (that is, how the substance is absorbed, distributed, metabolized, and excreted from the body) and (2) toxicodynamic differences (that is, the local biological effect(s) of the substance);

6.2.1.5 Estimating a NOAEL from a dose where adverse effects were observed (that is, LOAEL); and

6.2.1.6 When developmental toxicity data are not available.

6.2.2 These are the defined six (6) UFs for this practice. This practice only includes these six (6) UFs in the calculation, but it is recognized that there could be more or less used in the calculation.

NOTE 2—A NOAEL should only be used if it is lower than all LOAELs; otherwise, the lowest LOAEL must be used along with appropriate UFs. In this case, further assessment by a toxicologist to determine the applicability of the effect observed may be necessary.

NOTE 3—If regulatory limits for UFs already exist, it is the responsibility of the user of this standard to know which UFs are applicable in the jurisdiction where the product is to be distributed or sold, or both, and to comply with those requirements.

6.3 Determine the correction factors (CFs) necessary to convert POD values from one unit of measure to another and adjust non-continuous rates of change to continuous rates of change. For example, if the POD has units of mg/mL vapor per puff and the desired acceptable daily inhalation limit has units of mg/day, appropriate CFs must be applied.

6.3.1 CF categories may include:

6.3.1.1 Purity of the non-cannabinoid ingredient in the source material. Purity is typically expressed as a percentage or weight by weight measurement;

6.3.1.2 Body weight assumption of the target population;

(1) POD is oftentimes expressed as mg/kg body weight and needs to be multiplied by the target population body weight