Background and considerations for guidance on microbial and chemical contaminant tolerance limits

Controlled Substances and Cannabis Branch
Health Canada

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Canada

Background information on the proposed guideline tolerance limits for microbial and chemical contaminants in cannabis products

Note: For the specific limits in the current editions of the referenced publications, please see the table entitled "*Recommended contaminant publications and their limits*"

Background: Draft guidance for microbial and chemical contaminant tolerance limits

- Health Canada is currently developing a guidance document on microbial and chemical contaminant tolerance limits in cannabis products and is seeking feedback on its proposed guidance
  - Guidance will outline what limits are appropriate for most situations

- The guidance will identify example pharmacopoeial publications referred to in Schedule B of the *Food and Drugs Act* and describe how to use them
  - In particular, how to use general chapters and apply their concepts, as appropriate, to cannabis products

- Purpose of the guidance is to help:
  - Industry demonstrate compliance
  - Streamline inspections and licence reviews
  - Achieve the goals of protecting public health, public safety and ensuring access to a quality-controlled supply of cannabis under the *Cannabis Act*

Background: Engagement plan for draft guidance

- Health Canada is engaging stakeholders on its draft guidelines for microbial and chemical contaminant tolerance limits for various forms of cannabis products

- Purpose of engagement:
  - Present a table of example pharmacopoeial publications and their limits and solicit feedback from licence holders in order to:
    - Ensure the guidance document is sound and appropriate
    - Understand potential impacts to industry
    - Identify any gaps and concerns

Background

- The *Cannabis Act* aims to protect public health through strict safety and quality regulations for cannabis products

- Under the *Cannabis Regulations*, sections 93, 94, 101, 101.1 and 102.1 and/or their subsections require that microbial and chemical contaminants be within the tolerance limits found in a publication (pharmacopoeia) referred to in Schedule B of the *Food and Drugs Act*
  - Examples of the listed pharmacopoeias include the European Pharmacopoeia (Ph Eur) and United States Pharmacopeia (USP)

- The *Cannabis Regulations* also require that microbial and chemical tolerance limits be appropriate for the intended or reasonably foreseeable use of the cannabis product

Background

- The relevant publications in Schedule B of the *Food and Drugs Act* regarding contaminants and their limits take into account certain considerations such as production methods and product characteristics

- These pharmacopoeial publications and their tolerance limits are meant to:
  - Consider the intended or reasonably foreseeable uses for various cannabis product forms (the contaminant "exposure")
  - Take into account commonly adopted industry practices and what good quality assurance practices (e.g., compliant Good Production Practices) would be expected to achieve
  - Address potential gaps that may exist pertaining to safety and quality

Background

- In order to establish contaminant tolerance limits for specific cannabis product types, licence holders must determine product characteristics such as:
  - The health and safety risks inherent to the route of exposure
  - Anticipated daily consumption quantities sufficiently protective for consumers
  - What is reasonably achieved by compliant Good Production Practices (GPPs) for meeting the *Cannabis Act* objective of access to quality-controlled cannabis
  - Any special considerations for processing steps (e.g., if you use a solvent, you must demonstrate that any residues are at levels that are compliant)

Overview of and considerations for draft guideline tolerance limits for microbial and chemical contaminants in cannabis products

Note: For the specific limits in the current editions of the referenced publications, please see the table entitled "*Recommended contaminant publications and their limits*"

Draft guidelines: **Microbial contaminants**

Considerations:

- Pathogens and quality parameters should be appropriate to the intended use (e.g., topicals to use specifications for cutaneous products)
- Cannabis as a plant has a naturally-occurring bioburden, thus this must be taken into consideration for products such as dried cannabis and certain forms of extracts (e.g., kief)
- What GPPs might be reasonably expected to achieve with respect to contaminant levels (e.g., reduced microbial loads after certain processing steps)
- Tolerance limits for contaminants should align, unless otherwise specified by Health Canada, with limits for cannabis communicated by standards development organizations (e.g., USP)
- On a case-by-case basis, for some lots or batches of cannabis, maximum acceptable counts may be appropriate if justifiable for the method. Maximum acceptable counts have been established for the culture-based methods for total aerobic microbial count and total yeasts and moulds count referenced in the recommended publications

Draft guidelines: **Microbial contaminants**

Intended use	Product examples	Recommended Ph Eur publications	Recommended USP publications
Smoked or vaped	**Dried cannabis**	Ph Eur 5.1.8 - Table C	USP 2023 - Table 2, dried or powdered botanicals
	Extracts[1]	Ph Eur 5.1.4 - Inhalation use	USP 1111 - Inhalation use

[1]With certain exceptions for when the extract would be expected to retain the bioburden of dried cannabis (e.g., kief) and the limit for dried cannabis may be more appropriate

Draft guidelines: **Microbial contaminants**

Intended use	Product examples	Recommended Ph Eur publications	Recommended USP publications
Heatless inhaled products	Extract inhalers[1]	Ph Eur 5.1.4 - inhalation use	USP 1111 - inhalation use
	Inhaled nebulized liquid preparations and non-pressurized metered-dose liquid preparations that do not contain a preservative and do not have adequate antimicrobial properties	Ph Eur 0671 - sterile	USP 5 - sterile
Ingested products	Edible cannabis inputs[2] *Recommended limits only apply to input cannabis*	Ph Eur 5.1.8 - Table B or C[3]	USP 2023 - Table 2[4]

[1]Special requirements apply to liquid preparations for nebulization and non-pressurized liquid metered-dose preparations that do not contain a preservative and do not have adequate antimicrobial properties

[2]The *Cannabis Regulations* subsection 94(2) requires that the input cannabis be tested for edible cannabis products. While there is no finished product testing requirement for edible cannabis, s. 102.1(1) of the *Cannabis Regulations* require that the edible cannabis must not be prohibited under any of paragraphs 4(1)(a) to (d) of the *Food and Drugs Act*

[3]The user may choose to use Table B when the method of processing reduces the microbial levels to below those stated in that table, and Table C when the method of processing does not reduce the levels to below those stated in Table B

[4]The user is required to choose a specification in Table 2 based on the matrix that most closely corresponds to their input material

Draft guidelines: **Microbial contaminants**

Intended use	Product examples	Recommended Ph Eur publications	Recommended USP publications
Topicals	Creams, patches	Ph Eur 5.1.4 - cutaneous use Ph Eur 5.1.4 – transdermal patches	USP 1111 - cutaneous use USP 1111 - transdermal patches
Other	Nasal, oromucosal, gingival, vaginal, rectal, etc	Ph Eur 5.1.4 - as per the use that matches the intended use of the product. If one does not match exactly, then choose the most appropriate or an alternate specification and justify	USP 1111 - as per the use that matches the intended use of the product. If one does not match exactly, then choose the most appropriate or an alternate specification and justify

Draft guidelines: **Foreign matter (including visible mould)**

- The general chapter Ph Eur 2.8.2 for foreign matter requires that product be free of moulds, insects and other contamination (by naked eye or 6x magnification)

Intended use	Product examples	Recommended Ph Eur publications
All	Dried cannabis	Ph Eur 2.8.2

Draft guidelines: **Elemental impurities**

Considerations:

- Permitted daily exposure (PDE) for the heavy metals must not be exceeded
- Toxicity of the heavy metal contaminant depends on the route of exposure
- What GPPs might be reasonably expected to achieve with respect to elemental impurities
  - Guideline concentration limits are those found in Ph Eur 5.20 Table A.2.2 or A.5.2 and USP 232 Table 3 which are commonly adopted by industry
    - E.g., Table A.2.2 of Ph Eur 5.20 states: Permitted concentration for elemental impurities in products with a daily consumption amount of not more than 10 grams per day
  - Guideline concentration limits are also based on levels of elemental impurities observed in testing datasets and from concentration limit requirements in other jurisdictions as well as align with limits communicated by USP and Ph Eur

Draft guidelines: **Elemental impurities**

Considerations:

- One is expected to test, at the minimum, for Class 1 elemental impurities arsenic, cadmium, lead and mercury due to their ubiquity in the environment and the cannabis plant's ability to bioconcentrate metals

- As per the referenced Schedule B publications, when other elemental impurities are known to be present, have been added or have the potential for introduction (e.g., due to past or nearby industrial activities), one must also test for that metal or demonstrate any risk posed has been mitigated/controlled
  - E.g., See Ph Eur 5.20 Table 5.1 for guidance on which elemental impurities may be considered in a risk analysis for different modes of product consumption

Draft guidelines: **Elemental impurities**

Considerations:

- On a case-by-case basis, when the guideline concentration limit cannot be reasonably achieved with compliant GPPs, a less stringent limit that still respects the permitted daily exposure for that heavy metal may be applied

- Some product forms may have reasonably foreseeable consumption patterns that are greater than 10 g/day, which would result in the PDE being exceeded for some consumers
  - In such cases, keeping in mind that the PDE cannot be exceeded when determining the concentration limits, the reasonably foreseeable consumption amounts must be sufficiently high to protect the health and safety of the majority of consumers

- How concentration limits are derived from consumption levels is outlined in the referenced Schedule B publications:

Concentration limit (ug/g) = PDE (ug/day) ÷ daily amount (g/day)

Draft guidelines: **Elemental impurities**

Intended use	Product examples	Guideline concentration limit[1]	Recommended Ph Eur publications	Recommended USP publications
Smoked, vaped and inhaled	Vaping liquids, smoked/vaped concentrates and dried cannabis, inhalers/nebulizers	Guideline limit corresponds to Ph Eur 5.20 Table A.2.2 and USP 232 Table 3	Ph Eur 5.20 - inhaled use	USP 232 - inhaled use
Ingestion	Extracts (capsules, lozenge, other orally-ingested extracts)	Guideline limit corresponds to Ph Eur 5.20 Table A.2.2 and USP 232 Table 3	Ph Eur 5.20 - oral use	USP 232 – oral use
	Edible cannabis inputs[2]	Guideline limit for *the input* corresponds to Ph Eur 5.20 Table A.2.2 and USP 232 Table 3	Ph Eur 5.20 - oral use	USP 232 – oral use

[1]Concentration limits are appropriate for product forms where no more than 10 g consumed per day would be reasonably foreseeable for most consumers. For products whose reasonably foreseeable use exceeds 10 g per day, different concentration limits may be necessary in order to not exceed permitted daily exposures

[2]The *Cannabis Regulations* subsection 94(2) requires that the input cannabis be tested for edible cannabis products. While there is no finished product testing requirement for edible cannabis, s. 102.1(1) of the *Cannabis Regulations* require that the edible cannabis must not be prohibited under any of paragraphs 4(1)(a) to (d) of the *Food and Drugs Act*

Draft guidelines: **Elemental impurities**

Intended use	Product examples	Guideline concentration limit[1]	Recommended Ph Eur publications	Recommended USP publications
Topicals	Creams, patches	Guideline limit corresponds to Ph Eur 5.20 Table A.5.2 and USP 232 Table 3	Ph Eur 5.20 - cutaneous use	USP 232 - all categories of use are deemed sufficiently protective at this time, except antimony, where the parenteral or inhalation limit should be applied[2]
Other	Nasal spray, suppositories, etc	Guideline limit corresponds to Ph Eur 5.20 Table A.2.2 and USP 232 Table 3	Ph Eur 5.20 - choose the route of exposure that is most appropriate for the product in question. If one does not match, then one may use the concepts described in the publication to derive an appropriate PDE (see section 3.2 "Other Routes of Administration" of the Ph Eur 5.20 adopted ICH Q3D guideline)	USP 232 - choose the route of exposure that is most appropriate for the product in question. If one does not match, then one may derive an appropriate PDE for that use

[1]Limit applies for product forms where no more than 10 g consumed per day would be reasonably foreseeable for most consumers

[2]The toxicity from dermal exposure to antimony is higher than from oral exposure

Draft guidelines: **Residual solvents**

Considerations:

- Permitted daily exposure (PDE) for the solvents must not be exceeded

- The limits in the referenced Schedule B publications are appropriate for any route of exposure

- What GPPs might be reasonably expected to achieve with respect to levels of residual solvents
  - Guideline concentration limits for Class 2 residual solvents are found in column 3 of Table 2 of Ph Eur 5.4 and column 3 of Table 3 of USP 467
  - The guideline concentration limit for Class 3 residual solvents (Table 3 of Ph Eur 5.4 and Table 4 of USP 467) is 5000 ppm
  - Guideline concentration limits are also based on concentration limit requirements in other jurisdictions

Draft guidelines: **Residual solvents**

Considerations:

- On a case-by-case basis, when the guideline concentration limit cannot be reasonably achieved with compliant GPPs, a less stringent limit that still respects the permitted daily exposure for that solvent may be applied

- Some product forms may have reasonably foreseeable consumption patterns that are greater than 10 g/day, which would result in the PDE being exceeded for some consumers
  - In such cases, keeping in mind that the PDE cannot be exceeded when determining the concentration limits, the reasonably foreseeable consumption amounts must be sufficiently high to protect the health and safety of the majority of consumers

- How concentration limits are derived from consumption levels is outlined in the referenced Schedule B publications:

Concentration limit (ug/g) = PDE (ug/day) ÷ daily amount (g/day)

Draft guidelines: **Residual solvents**

Intended use	Product examples	Guideline concentration limit[1]	Recommended Ph Eur publications	Recommended USP publications
All	Any product with use of solvents in their processing or where solvents are likely to be present[2,3]	- Class 1 Solvents should be avoided - Class 2 solvents should be limited - Limit for Class 3 solvents is 5000 ppm[4]	Ph Eur 5.4	USP 467

[1]Concentration limits are appropriate for product forms where no more than 10 g consumed per day would be reasonably foreseeable for most consumers. For products whose reasonably foreseeable use exceeds 10 g per day, different concentration limits may be necessary in order to not exceed permitted daily exposures

[2]Testing and limits are only required for solvents that are used in the production of, or are likely to contaminate, the product

[3]The *Cannabis Regulations* subsection 94(2) requires that the input cannabis be tested for edible cannabis products and the guideline concentration limit applies to the input cannabis for edible cannabis products. While there is no finished product testing requirement for edible cannabis, s. 102.1(1) of the *Cannabis Regulations* require that the edible cannabis must not be prohibited under any of paragraphs 4(1)(a) to (d) of the *Food and Drugs Act*

[4]Health Canada currently considers butanes and propane as class 3 solvents

Draft guidelines: **Mycotoxins**

- The limits in the referenced publications are independent of consumption amounts or routes of exposure

Intended use	Product examples	Recommended Ph Eur publications	Recommended USP publications
All	All products[1]	Ph Eur 2.8.18	USP 561

[1]The *Cannabis Regulations* subsection 94(2) requires that the input cannabis be tested for edible cannabis products. While there is no finished product testing requirement for edible cannabis, s. 102.1(1) of the *Cannabis Regulations* require that the edible cannabis must not be prohibited under any of paragraphs 4(1)(a) to (d) of the *Food and Drugs Act*

Draft guidelines: **Other considerations**

- Pharmacopoeias do not address every contaminant and/or have specific tolerance limits for every potential contaminant
- Licence holders are also responsible for ensuring their products do not contain unacceptable levels of such other[1] microbial or chemical contaminants as outlined in sections 93, 94, 101, 101.1 and 102.1 and/or their subsections of the *Cannabis Regulations*
- Such contaminants may include, but are not limited to:
  - Impurities of chemical or biochemical synthesis of cannabinoids (as outlined, for example, in Ph Eur 2034 or USP 476)
  - Microorganisms not specifically identified in the microbial contaminant general chapters
  - Physical contaminants, such as foreign matter

[1]Licence holders are expected to test for these other microbial and chemical contaminants when there is a risk or likelihood of it contaminating their cannabis products (e.g., as identified via a preventive control plan)

Draft guidelines: **Other considerations**

- If you become aware of a contaminant in the cannabis you are testing that is not on its specification sheet, these cannot be overlooked, and you must still ensure the quality of the cannabis
  - For example, you may choose to add an appropriate limit for the contaminant to your product specification sheet or address the contamination via a corrective action and preventive action plan or otherwise justify the action taken when becoming aware of the test result

To facilitate your feedback, Health Canada has prepared the following questions:

- Do you agree that the recommended contaminant publications and their associated limits are appropriate for the various forms of cannabis products? If no, please explain, including any specific concerns you may have or problematic areas you may have identified.

- Is the information sufficiently comprehensive or has a product form (or associated intended use), publication or tolerance limit been missed? If so, please provide details, including whether any other information found in the publications listed in Schedule B of the Food and Drugs Act should be included in the guidance.

- Are you aware of other information, data, analyses, reports, issues or concerns related to chemical and microbial contaminant tolerance limits that you would like to share with Health Canada?

How to submit your feedback

- Please provide your **responses** and **feedback** to the engagement materials by **the end of December 2023**

- Your **responses** and **feedback** to the engagement materials can be sent to:
  - Email address:
    cannabis.science.engagement-mobilisation.science.cannabis@hc-sc.gc.ca
  - Subject line for responses/feedback:
    Health Canada's public engagement on microbial and chemical contaminant limits for cannabis products
  - For questions or clarifications, please use the following subject line:
    Question or clarification required