

CODEX ALIMENTARIUS COMMISSION



Food and Agriculture
Organization of the
United Nations



World Health
Organization

E

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

CL 2026/10-RVDF

January 2026

TO: Codex Contact Points
Contact Points of international organizations having observer status with Codex

FROM: Secretariat, Codex Alimentarius Commission,
Joint FAO/WHO Food Standards Programme

SUBJECT: Request for comments at Step 6 on maximum residue limits for veterinary drugs in foods:
MRLs for fumagillin dicyclohexylamine (DCH) in finfish (fillet) and honey

DEADLINE: 28 February 2026

BACKGROUND

MRLs for fumagillin dicyclohexylamine (DCH) in finfish (fillet) and honey

Discussion at JECFA98

1. The 98th Meeting of the Joint FAO/WHO Expert Meeting of Food Additives (JECFA98, 2024) was part of a series of similar meetings specifically convened to consider residues of veterinary drugs in food. The tasks before the Committee were to elaborate further principles for evaluating the safety of residues of veterinary drugs in food, to establish acceptable daily intakes (ADIs) and acute reference doses (ARfDs), to recommend maximum residue limits (MRLs) for such residues when the drugs under consideration are administered to food-producing animals in accordance with good practice in the use of veterinary drugs (GVP); to evaluate the safety of residues of certain veterinary drugs; and to respond to specific requests from the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF).¹
2. JECFA98 evaluated the safety of two veterinary drugs, clopidol and fumagillin dicyclohexylamine (DCH).
3. The meeting report is published in the WHO Technical Report Series (TRS 1055). Toxicological monographs summarizing the data considered by JECFA98 in establishing ADIs will be published in the WHO Food Additives Series No. 89. Residue monographs summarizing the data considered by JECFA98 in recommending MRLs will be published in FAO JECFA Monographs No. 33. The summary report² of JECFA98 is available on the FAO and WHO webpages for consultation. The full report³ of JECFA98 is available on the WHO webpage for consultation.

Discussion at CCRVDF27

4. The 27th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF27, 2024) considered the MRLs for fumagillin DCH and had a lengthy discussion on the appropriateness of using DCH as the marker residue for fumagillin in the aforesaid commodities, which are summarized below. The whole discussion is available in the report⁴ of the session.
5. Several member countries and organizations raised significant concerns about using DCH as a residue marker in honey. DCH is not a unique marker for fumagillin; it can originate from environmental and industrial sources, complicating regulatory compliance and potentially leading to misinterpretation of fumagillin use in food products. There were also concerns that if other fumagillin salts are used in the future, DCH would no longer be an appropriate marker. Additionally, the absence of comprehensive toxicology, metabolism, and residue-depletion data created uncertainty about the safety assessment, prompting some members to withhold support for the proposed MRLs until additional regional data and a review of JECFA monographs are available.

¹ JECFA documents, e.g., reports, monographs, etc., are available on the FAO and WHO websites as follows:

- FAO: <https://www.fao.org/food-safety/scientific-advice/jecfa/en/>
- WHO website: [https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-\(jecfa\)https://openknowledge.fao.org/server/api/core/bitstreams/03c7c879-e048-4452-833a-28ae6a13fb3e/content](https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)https://openknowledge.fao.org/server/api/core/bitstreams/03c7c879-e048-4452-833a-28ae6a13fb3e/content)

² <https://www.who.int/publications/i/item/9789240095533>

³ <https://www.who.int/publications/i/item/9789240095533>

⁴ [REP24/RVDF27](#), paragraphs 39-49, 53

6. CCRVDF considered several proposals to address the challenges with marker selection, risk assessment, and the establishment of MRLs for fumagillin DCH.
7. For honey, since fumagillin is not a stable marker, DCH was proposed as the only viable marker, with the rationale that residues from good veterinary practice would remain below the MRL, and environmental sources would be unlikely to cause exceedances. Other suggestions included adding a note to clarify DCH's non-uniqueness and, alternatively, using fumagillin itself as the marker with an MRL set at twice the limit of quantification, aligning with previous committee decisions and supported by Canadian research.
8. For fish, it was proposed to advance the MRL based on the equimolar relationship between fumagillin and DCH, allowing for a scientifically justified back-calculation from the Acceptable Daily Intake, demonstrating that potential DCH levels in fish would be well below any risk threshold, which would ensure a conservative and protective residue limit.
9. The proposals were not supported primarily due to insufficient monitoring data to assess the impact of environmental sources of DCH, which could lead to regulatory challenges if MRLs were exceeded. Moreover, previous experience indicated that simply adding a note about DCH's non-uniqueness was ineffective in resolving trade issues or preventing the rejection of compliant products. Compounding these concerns, fumagillin's instability in honey rendered it unsuitable as a marker residue. At the same time, additional evidence was needed to justify that the residue depletion kinetics of fumagillin and DCH would be the same. Unresolved questions regarding the compound's toxicology and residue assessment further underscore the need for further investigation. Additionally, it was noted that for many compounds, markers are used even when residues are not expected, and MRLs have been established without the marker needing to be present, raising further questions about why DCH—despite not being a unique marker—was chosen over fumagillin as the alternate marker in this case.
10. The FAO JECFA Secretariat explained the reasoning behind JECFA's recommendations despite the limited available information (as also outlined in the JECFA98 report, monographs, and CRD08) as follows:
 - Limited options were available to JECFA because fumagillin was not a stable marker in honey; therefore, JECFA recommended DCH as the marker residue in honey. JECFA had reviewed information on potential sources of environmental contamination, but could not determine how much would be transferred to honey.
 - It was assumed that if the compound was used according to good veterinary practices (GVPs), the residues would be below the proposed MRL, and it was also noted that CCRVDF might consider different risk management decisions, for example, in selecting alternative marker residues for monitoring.
 - CCRVDF26 requested that JECFA specifically assess fumagillin DCH rather than a different salt and that, as far as JECFA was aware, fumagillin was only used in this specific salt form.
 - More data is needed to address Members' comments and concerns.
11. The WHO JECFA Secretariat provided the following clarification in response to comments regarding the data gaps in the toxicological data for assessing fumagillin DCH:
 - The toxicological data package submitted for fumagillin DCH was incomplete. However, using the risk analysis decision tree, JECFA reached conclusions on acceptable levels of residues of fumagillin and DCH arising from its use as a veterinary drug.
 - Sub-chronic studies in rats were available for both fumagillin DCH and DCH. Although JECFA was unable to assess carcinogenic hazard definitively from the data available, based on the lack of genotoxicity of either fumagillin DCH or DCH in reliable studies and the absence of preneoplastic changes after their sub-chronic administration, JECFA was able to conclude on the likely risk of carcinogenicity on exposure to residues of either moiety. This was similar to the approach proposed by several risk assessment bodies, such as the United Kingdom Committee on Carcinogenicity¹², and the Organization for Economic Cooperation and Development.
 - In relation to reproductive toxicity testing, only developmental toxicity studies were available for fumagillin DCH, but a screening-level reproductive toxicity study was available for DCH. Information on toxicity (or the lack thereof) to reproductive organs was available for both compounds from the 90-day studies. Hence, using an approach similar to that used to assess the risk of carcinogenicity, JECFA concluded that although no definitive conclusion on hazard could be reached, it was possible to assess the likely risk of reproductive toxicity from exposure to residues of fumagillin and DCH.

- No chronic toxicity studies were available, but using an additional uncertainty factor (typically 3) to the point of departure from a 90-day study to cover this data gap would be common practice.
 - Sub-acute clinical trials (2-4 weeks with follow-up) in human subjects were also available for fumagillin. Hence, JECFA was of the view that overall, the application of a safety factor of 5 would cover the uncertainties associated with the lack of some studies, including in dogs.
12. Given the questions and concerns expressed by Members, the Chairperson indicated that the Risk Analysis Principles applied by CCRVDF allowed for the submission of concern forms (CFs) up to one month after the end of the session. The CF provides for the submission of specific questions or concerns, including data and/or information, on the risk assessment process that led to the establishment of the MRL for consideration by JECFA. This would also improve communication between CCRVDF and JECFA.
13. A concern form was subsequently received from the United States of America and Canada, which is attached to this circular letter for information (Appendix III).

REQUEST FOR COMMENTS

14. Codex members and observers, who may wish to expand on or complement the comments and questions presented in the concern form of Canada/USA, or provide additional comments or questions related to other specific issues, should do so while providing the relevant rationale accompanied by applicable data/information if appropriate, and if possible, confirmation of the timing of data availability.
15. If appropriate, Codex members can support their questions by submitting concern forms in accordance with the template provided in Annex B of the *Risk Analysis Principles applied by CCRVDF* as set out in the Procedural Manual of the Codex Alimentarius Commission and reproduced in Appendix II for convenience.
16. Submission of concern forms in support of additional questions (other issues not identified in the CF of Canada/USA) will facilitate consideration of this matter by CCRVDF, i.e., to better frame the request for risk assessment by JECFA, their prioritization for re-evaluation by JECFA under Agenda item 10, and the subsequent consideration of the MRLs by JECFA at its next meeting.

GUIDANCE ON THE PROVISION OF COMMENTS

17. Comments should be submitted through the Codex Contact Points of Codex members and observers using the OCS.
18. Contact Points of Codex members and observers may log in to the OCS and access the document open for comments by selecting "Enter" in the "My reviews" page, which is available after logging in to the system.
19. Contact Points of Codex members and observers' organizations are requested to provide proposed changes and relevant comments/justifications on a specific paragraph (under the categories: editorial, substantive, technical, and translation) and/or at the document level (general comments or summary comments). Additional guidance on the OCS comment categories and types can be found in the OCS [Frequently Asked Questions \(FAQs\)](#).
20. Other OCS resources, including the user manual and short guide, can be found at the following link: <http://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/>.
21. For questions on the OCS, please contact Codex-OCS@fao.org.

APPENDIX I
MRLS FOR FUMAGILLIN DCH IN FINFISH (FILLET) AND HONE
(For comments at Step 6)

FUMAGILLIN DICYCLOHEXYLAMINE (DCH) (mycotoxin)

Fumagillin is administered only as dicyclohexylamine (DCH) salt in veterinary medicine. As the fumagillin DCH salt dissociates into the two moieties, consumers would be exposed to residues of both. JECFA98 (2024) evaluated both fumagillin and DCH.

For information

JECFA evaluation	98 (2024)
Acceptable daily intake	For fumagillin 0–0.003 mg/kg bw based on a no-observed-adverse-effect level (NOAEL) of 1.73 mg/kg bw per day for decreased body weight gain in a 13-week study in rats and for post-implantation loss, decreased fetal body weight, and associated morphological changes in a developmental toxicity study in rats at 4.32 mg/kg bw per day. A safety factor of 500 was used, which comprised 100 for interspecies and intraspecies differences and an additional factor of 5 for database uncertainty. For DCH 0–0.02 mg/kg bw based on a NOAEL of 10 mg/kg bw per day for haematological and clinical chemistry changes at 30 mg/kg bw per day in a 13-week toxicity study in rats. A safety factor of 500 was used, which comprised 100 for interspecies and intraspecies differences and an additional factor of 5 for database uncertainty.
Acute reference dose	For Fumagillin, an ARfD is unnecessary. For DCH, 0.7 mg/kg bw based on the NOAEL of 70 mg/kg bw per day for clinical signs and mortality after 4 days at 200 mg/kg bw per day in a 28-day toxicity study in rats. A safety factor of 100 was used to allow for interspecies and intraspecies differences.
Estimated chronic dietary exposure	Based on potential fumagillin residues in fish fillet and honey, the global estimates of chronic dietary exposure (GECDEs) are: <ul style="list-style-type: none"> • For adults and the elderly, 0.06 µg/kg bw per day. • For children and adolescents, 0.10 µg/kg bw per day. • For infants and toddlers, 0.11 µg/kg bw per day. (representing 2%, 3%, and 4%, respectively, of the upper bound of the ADI of 3 µg/kg bw)
Residue definition	The marker residue for fumagillin DCH in fish fillet is fumagillin. The marker residue for fumagillin DCH in honey is dicyclohexylamine (DCH).

For comments

Maximum residue limits (MRLs)

Species	Fillet (µg/kg)	Notes
Fish	10 (For the marker residue (MR) fumagillin)	Residues of DCH (including any potential metabolites) should be monitored when fumagillin DCH preparations are used in fish to ensure that the concentration is < 1000 µg/kg, a target level compatible with the upper bound of the ADI. A suitable analytical method for determining DCH in fish fillets would need to be developed. (JECFA98, 2024)

Species	Honey (µg/kg)
-	20 (For the marker residue (MR) DCH)

APPENDIX II**TEMPLATE FOR THE SUBMISSION OF CONCERN FORMS**

(To be submitted in reply to this CL in support of the questions submitted in paragraph 14 of CL 2026/10-RVDF, to support additional questions, to indicate data/information availability and timing)

1. Submitted by: (name of the delegation)
2. Date:
3. Veterinary drug:
4. Commodity (species and tissues):
5. MRL (mg/kg):
6. Present step:
7. Description of the concern:
8. Summary of the supporting documentation that will be submitted to JECFA (e.g., toxicology, residue, microbiology, dietary exposure assessment):

APPENDIX III
(Available in English only)
CONCERN FORM SUBMITTED BY CANADA AND THE UNITED STATES OF AMERICA
(For information)

**CONCERN FORM SUBMITTED BY THE UNITED STATES OF AMERICA AND CANADA FOR MAXIMUM RESIDUE LIMITS
RECOMMENDED BY THE 98TH MEETING OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES FOR
FUMAGILLIN DICYCLOHEXYLAMINE IN FISH FILLET AND HONEY**

Submitted by: United States of America and Canada

Date: 08 November 2024

Veterinary Drug: Fumagillin dicyclohexylamine (DCH)

Commodity (species and tissues): Fish (fillet) and honey

MRL ($\mu\text{g}/\text{kg}$): Fumagillin: 10 $\mu\text{g}/\text{kg}$ in fish fillet

DCH: 20 $\mu\text{g}/\text{kg}$ in honey

Present step: 6 (for comments) and 7 (for consideration by CCRVDF28 in 2026)

Description of the concern:

The United States and Canada have reviewed the report and the FAO monograph from the 98th JECFA meeting where the Committee established health-based guidance values (HBGVs) and maximum residue limits (MRLs) for fumagillin DCH. We note that, because the report provides only a summary of the toxicological studies, the details regarding the hazard assessment are not fully described. Nevertheless, based on the available information, we suggest that JECFA request comprehensive, high-quality dossiers to enable robust risk assessments and risk management recommendations. The approach used by JECFA in the Guidance for the safety evaluation of residues of veterinary drugs with incomplete data packages should be used in very limited situations as outlined in the guidance. Although JECFA indicated that this Guidance was used when recommending HBGVs and MRLs for fumagillin DCH, the overall approach used for fumagillin DCH does not follow the practices used in current, modern risk assessments, including those outlined as harmonized procedures in VICH and OECD documents. Specifically, for fumagillin DCH, there is a lack of several critical toxicology, metabolism, and residue chemistry studies that are generally recognized as needed for contemporary risk assessments. Additionally, the marker residue selected for fumagillin DCH in honey is not a unique marker; therefore, when monitoring honey, it will not be known if the source of DCH in honey is from use of fumagillin DCH as a veterinary drug or from other sources. This can cause trade disruptions for honey as noted by multiple delegations at CCRVDF27. We recommend that JECFA provide a list of studies and data needed to conduct a robust risk assessment for fumagillin DCH that has less uncertainty. Below are our specific concerns based on the information available in the report and FAO monograph.

Toxicology

The data package provided to the JECFA was very limited which resulted in significant data gaps. The studies that are typically conducted for the assessment of veterinary drug residues in food were not conducted for fumagillin or DCH, including a chronic oral toxicity study, and studies to properly evaluate any potential concerns for reproductive safety to consumers. Additionally, all studies were conducted in rats which provides a limited view of the potential toxicity of fumagillin and DCH.

Acceptability of using a 90-day study instead of a chronic toxicity study or not requiring a study in a non-rodent species without validated alternative approaches does not allow for the proper evaluation of a compound. The Committee noted the database had uncertainty and added an additional factor of 5 in the calculation; however, some of the basic tests needed to conduct the human food safety evaluation were not available. Based on the mode of action, fumagillin inhibits type 2 methionine aminopeptidase, which affects translation of downstream proteins regulated by eukaryotic initiation factor-2a, involved in many functions such as angiogenesis; therefore, it is important to characterize the potential systemic effects of chronic exposure.

Clinical concentrations of fumagillin used in humans were only administered for up to two weeks, and in those studies, reversible hematological changes were noted even when humans were exposed for a short treatment of duration. Therefore, these studies are not representative of chronic exposure resulting from residues of fumagillin and DCH in food. Consumers can be exposed to fumagillin DCH every day of their lives, and there is no information on the chronic exposure to consumers as well as any potential effects to those which are in reproductive age. The Committee did not thoroughly explain how the factor of 5 was determined to be adequate when substituting the 90-day rodent toxicity test *in lieu* of conducting a chronic toxicity test.

The Committee concluded that, in the absence of genotoxicity and other effects on reproductive organs, residues of fumagillin in the diet from its use as a veterinary drug are unlikely to cause effects on reproduction or on the offspring. However, the information used to make this conclusion was based on only a very limited data set. Using information regarding the genotoxicity or information from repeat-dose studies instead of conducting reproductive studies, leaves a major data gap. The aim of reproductive toxicity testing is to identify possible adverse effects of a substance on any part of this reproductive cycle, including the impairment of the reproductive function in males and females, as well as the effects on the fetus or offspring. Applying uncertainty factors to address the lack of data may not be reliable.

The Committee noted that no data on the metabolism or kinetics of fumagillin in mammalian species was available, only the degradation in honey. This adds additional uncertainty to whether the toxicity for the compounds and its metabolites have been fully characterized. The Committee noted that based on structural considerations they concluded that the degradation products are unlikely to be of greater toxicological concern than fumagillin; however, the details were not described on how this conclusion was made.

For DCH, pharmacokinetic data was found in the public literature indicating that DCH is rapidly absorbed in rats and rabbits after administration by oral gavage. JECFA reported that DCH is extensively metabolized *in vitro*; however, there was no metabolite identification.

Subchronic rat toxicity studies conducted with DCH noted a decrease in ovarian weights and increased testicular weight in a screening test for reproductive toxicity. Additionally, increased stillborn pups, decreased number of liveborn pups, and a reduction in pup weights were also noted in the summary of the preliminary screen. These results bring in question whether further reproductive toxicity testing should be conducted. The GLP reproductive toxicity study was noted as a preliminary test; however, the limitations of the study were not explained.

The ARfD established for DCH was based on mortality noted after 4 days of administration at a dose of 200 mg/kg bw/day, in a repeated dose oral toxicity conducted in rats for 28-days. However, details on which early endpoints were measured in the study were not provided to understand if the NOEL and safety factor selected were appropriate.

Therefore, because of the limited data and information regarding the toxicity of fumagillin and DCH, it is not feasible to determine if the safety factors selected for the ADI for fumagillin and the safety factors selected for the ADI and ARfD for DCH are sufficient to alleviate potential toxicological concerns.

Residue Metabolism and Depletion

Metabolism

- No data were provided on the metabolism of DCH in fish. Metabolism data are needed to conduct a risk assessment for compounds of toxicological concern to identify toxicologically relevant metabolites and to enable a comparative metabolism evaluation between the target animal species and the species used in the toxicological testing.
 - Without DCH metabolism data in fish and based on the data reported in rabbits and rats demonstrating metabolism of DCH, how did the Committee conclude that there are no DCH metabolites of toxicological concern present in fish fillet?
- The monograph states that almost 50% of the radioactive residues of fumagillin could not be extracted from fish fillet, and that only parent fumagillin was identified in the radioactive residues in fish fillet. Based on these findings, the Committee concluded that fumagillin was not metabolized.
 - If approximately 50% of radioactive residues were extracted and characterized, then approximately 50% were not extracted and characterized. Because extractability is influenced by the physico-chemical properties of a compound, the large ratio of unextracted residues suggests that the unextracted residues were chemically different from parent fumagillin. Knowing that approximately 50% of the radioactive residues were not extracted and characterized, how did the Committee conclude that fumagillin is not metabolized and that there were no metabolites of toxicological concern in the unextracted radioactive residues in fish fillet?
- The monograph states that the tritium radiolabel was unstable during the fumagillin metabolism study in fish.
 - An unstable tritium label suggests that residues of fumagillin could have been present but not detectable because of label loss. How did the Committee determine that the measurements of total fumagillin residues and potential metabolites were accurate? In other words, how did the Committee determine that the measurement of total residues and potential metabolites was not an underestimate of total residue concentrations or that metabolites were not detected because of lost tritium label?

- The monograph states that, for the fumagillin metabolism study in fish, fumagillin “was randomly labelled with tritium; as such, the precise positions of the tritium labels in the fumagillin molecule were unknown.”
 - Current internationally harmonized guidance on metabolism studies calls for the radiolabel site to be a metabolically stable position to ensure that the portions of the parent drug that are likely to be of toxicological concern are labeled and, thus, measured.¹ If the site of tritium label was unknown, how did the Committee determine that portions of parent fumagillin that are likely to be of toxicological concern were labeled and monitored?
 - Did the random labeling of tritium refer to only the fact that the site was unknown, or did it also refer to an unknown number of labeling sites *per* molecule of fumagillin also? If the number of labeling sites *per* molecule of fumagillin was unknown, how was this taken into account when determining total residue concentrations in tissues based on the measured radioactivity and reported specific activity of the test article, because using specific activity typically requires the number of labeling sites *per* molecule to be known?
- The monograph states that no data were provided to the Committee, or available from the published literature, to allow comparison of metabolism between species. The purpose of a comparative metabolism evaluation is to determine if the laboratory animals used for toxicological testing have been exposed to the metabolites that humans can be exposed to from consumption of tissues obtained from treated animals.² This provides the scientific link between the residue data in the target animal species and the toxicological data in the laboratory species.
 - Without comparative metabolism data for fumagillin and DCH, how did the Committee conclude that the laboratory animals used for toxicological testing (in this case, rats) have been exposed to the same metabolites that humans can be exposed to from consumption of fillet from treated fish?

Residue Depletion

- The monograph states that no marker residue or total residue data were submitted for DCH in fish.
 - Without residue data for DCH in fish, how did the Committee estimate the amount of DCH residues present in fish fillet when Good Veterinary Practices (GVP) are followed?
- The monograph reports results from a residue depletion study in honey. Both parent fumagillin and parent DCH were measured. The monograph states, “Validation of the analytical method provided by the sponsor was insufficiently described for fumagillin, and no description of the method and no validation data were available for DCH.”
 - Without acceptable method validation data, how did the Committee determine that the data generated in honey are accurate and suitable for use in a risk assessment?
- The aforementioned residue depletion study in honey was not conducted according to GVP. The applied dosages were reported to be lower (75.6–98.6 percent) than the intended doses, and the treatment duration (4–5 weeks) was shorter than that approved according to GVP (6–8 weeks). Treatment was administered in spring, 1 month before onset of honey flow, and honey samples were taken starting 1 week after onset of honey flow (although GVP requires that the treatment should be finished 4 weeks (28 days) before the start of honey flow). The study indicated that residues of fumagillin and DCH remained quantifiable in honey up to 36 and 42 days, respectively, following the cessation of treatment.
 - In light of the study described above, and in the absence of a residue depletion study conducted according to GVP, how did the Committee conclude that residues of fumagillin and DCH would not be present in honey when fumagillin DCH is used according to GVP?

Marker Residue and Maximum Residue Limits

- The Glossary of Terms used by CCRVDF (CXA 5-1993) defines a marker residue as, “A residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk or other animal tissues. A specific quantitative analytical method for measuring the concentration of the residue with the required sensitivity must be available (See Note 3).”³

¹ VICH GL46: Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Metabolism Study to Determine the Quantity and Identify the Nature of Residues.

² VICH GL47: Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Laboratory Animal Comparative Metabolism Studies.

³ [Glossary of Terms and Definitions \(Residues of Veterinary Drugs in Foods\)](#)

As noted in the monograph, fumagillin DCH dissociates into the two moieties, meaning that consumers would be exposed to both fumagillin residues and DCH residues. Therefore, in the case of fumagillin DCH, total residues include residues of fumagillin and residues of DCH. The monograph states that parent fumagillin is a suitable marker residue for use of fumagillin DCH as a veterinary drug in fish. However, in fish, no residue data were submitted for DCH.

- How did the Committee determine that parent fumagillin is an appropriate marker residue for residues of fumagillin DCH in fish fillet if no data were provided that enabled the relationship between parent fumagillin and total residues of DCH to be established?
- The Committee recommended an MRL of 20 µg/kg for DCH in honey. The monograph states that GVP for fumagillin DCH require treatment to be completed 4 weeks prior to the start of honey flow, meaning that, under GVP, honey could be produced for human consumption as soon as 4 weeks after final treatment. The monograph describes a study that provided data on concentrations of DCH at approximately 4 weeks after final treatment (31 days). Although the study was not conducted entirely consistent with GVP because treatment started 1 month prior to honey flow, this time point (4 weeks after final treatment) roughly corresponds to the earliest time that honey could be produced for human consumption after treatment under GVP. At this time point, the concentration of DCH was reported to be 524.9 ± 261.5 µg/kg in honey.
 - Considering the available DCH residue data in honey at approximately 4 weeks after final treatment (524.9 ± 261.5 µg/kg) and knowing that there can be variability in determining when honey flow will begin, how did the Committee determine that a suitable MRL value is 20 µg/kg, and that this MRL value would not result in compliance issues when fumagillin DCH is used according to GVP?
- In Canada's experience, residues of DCH are routinely detected in honey when fumagillin is not present or has been confirmed to have not been used. A number of peer-reviewed journal articles support these findings and indicate that DCH residues in honey may be related to environmental contamination from the use of the compound in industrial applications^{4,5,6} (acknowledged by JECFA in CRD08 provided to CCRVDF27⁷). There is concern that the use of DCH as a non-specific marker residue may cause regulatory compliance issues, as food safety regulators may not be sure of the source of DCH, which may lead to incorrect conclusions about the use of fumagillin.
 - Considering that residues of DCH in honey may not be attributed to the use of fumagillin DCH alone, how did the Committee conclude that environmental sources of DCH would not directly result, or contribute, to the exceedance of the proposed MRL for honey?

Analytical Methods

- The monograph states, "the information on the performance of the analytical methods for fumagillin in fish and honey consisted only of a summary of validation data, making it difficult to confirm whether the methods adhered to full validation parameters in accordance with Codex Guideline CAC/GL 71-2009 or VICH guidelines. The Committee considered that, while the lack of full validation reports was a source of uncertainty, the methods were suitable for monitoring purposes."
 - If it was difficult to confirm whether the methods adhered to full validation parameters in accordance with Codex Guideline CAC/GL 71-2009 or VICH guidelines, how did the Committee determine that the methods were suitable for monitoring purposes?
- The monograph does not mention the availability of an analytical method for monitoring DCH residues in fish. Nevertheless, the Committee recommended monitoring DCH in fish fillet to ensure that the concentration does not exceed 1000 µg/kg.
 - How are competent authorities to monitor for DCH if the availability of an analytical method suitable for monitoring is uncertain?

⁴ van den Heever, J.P., Thompson, T.S., Curtis, J.M. & Pernal, S. F. (2015) Determination of Dicyclohexylamine and Fumagillin in Honey by LC-MS/MS. *Food Anal. Methods* 8, 767–777 (2015). doi: <https://doi.org/10.1007/s12161-014-9956-x>

⁵ van den Heever, J. P., Thompson, T. S., Curtis, J. M., & Pernal, S. F. (2015). Stability of dicyclohexylamine and fumagillin in honey. *Food Chemistry*, 179, 152-158. doi: <http://dx.doi.org/10.1016/j.foodchem.2015.01.111>

⁶ van den Heever, J. P., Thompson, T. S., Otto, S. J. G., Curtis, J. M., Ibrahim, A., & Pernal, S. F. (2016). The effect of dicyclohexylamine and fumagillin on *Nosema ceranae*-infected honey bee (*Apis mellifera*) mortality in cage trial assays. *Apidologie*, 47, 663-670. doi: [10.1007/s13592-015-0411-9](https://doi.org/10.1007/s13592-015-0411-9)

⁷ RVDF27/CRD08

Dietary Exposure

- The Committee used values of 5 µg/kg and 10 µg/kg to estimate the dietary exposure to fumagillin and DCH residues in honey, respectively. As described previously, although a study conducted entirely consistent with GVP was not provided, a study was provided that reported fumagillin and DCH concentrations in honey 31 days after treatment, which roughly corresponds to the earliest time point that honey could be produced for human consumption after treatment under GVP. At 31 days after treatment, fumagillin was reported at a concentration of 19.01 ± 10.00 µg/kg, and DCH was reported at a concentration of 524.9 ± 261.5 µg/kg in honey.
 - Considering the available fumagillin (19.01 ± 10.00 µg/kg) and DCH (524.9 ± 261.5 µg/kg) residue data in honey at approximately 4 weeks after treatment and knowing that there can be variability in determining when honey flow will begin, how did the Committee determine that the exposure values under GVP can be estimated to be 5 µg/kg for fumagillin and 10 µg/kg for DCH in honey?
- When considering dietary exposure to DCH from fish and honey, the Committee determined that up to 1000 µg/kg DCH could be present in fish fillet without causing an exceedance of the ADI. Therefore, the Committee recommended that fish be monitored for DCH to ensure that the concentration does not exceed 1000 µg/kg. The equation reported in the monograph that was used to determine this target level of DCH did not include any correction for the M:T ratio. That is, the equation assumed a M:T ratio of 1.
 - In the absence of metabolism data for DCH in fish, how did the Committee determine that the M:T ratio of DCH in fish fillet is equal to 1?

Summary of the supporting documentation that will be submitted to JECFA:

Canada will provide residue monitoring data for fumagillin and DCH in honey, obtained from a provincial government laboratory in Canada. The laboratory utilizes a validated LC-MS/MS method having LOQs of 0.005 µg/g for each analyte and LODs of 0.0017 and 0.0014 µg/g for fumagillin and DCH, respectively. A summary of the monitoring results for samples obtained from November 2023 to September 2024 are presented in the table below. In addition, raw data values for each honey sample analyzed are provided in the Excel spreadsheet titled “Fumagillin and DCH in Honey – Provincial Test Results.xlsx”.

Compound	# Samples Tested	# Samples <LOQ of 5 µg/kg	# Samples from 5 to 20 µg/kg	# Samples > 20 µg/kg	# Samples > 25 µg/kg	Maximum Concentration (µg/kg)	Median Concentration (µg/kg)	90th Percentile Concentration (µg/kg)
Fumagillin	411	387	23	1	1	63	<5	<5
DCH	411	165	173	73	49	200	7	26

Based on these monitoring results, Canada and the United States respectfully ask JECFA to reconsider their MRL recommendation for honey and to ask for additional studies to identify a suitable marker residue and MRL value that are consistent with GVP.

Additional information: *Fumagillin and DCH in honey – provincial test results* (English only):

[https://www.fao.org/fileadmin/user_upload/codexalimentarius/doc/Fumagillin and DCH in Honey-Provincial Test Results.xlsx](https://www.fao.org/fileadmin/user_upload/codexalimentarius/doc/Fumagillin_and_DCH_in_Honey-Provincial_Test_Results.xlsx)