



JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

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**MRLS FOR VETERINARY DRUGS ARISING FROM JECFA98 (2024)
MRLS FOR FUMAGILLIN DICYCLOHEXYLAMINE (DCH) IN FISH (FILLET) AND HONEY (AT STEP 7)**

Comments in reply to CL 2026/10-RVDF

*Comments by Canada, Ecuador, the European Union (EU), Guatemala,
Indonesia, Malaysia, Panama, Qatar, Senegal, United Arab Emirates (UAE), United Kingdom*

Background

1. This document compiles comments received through the Codex Online Commenting System (OCS) in response to CL 2026/10-RVDF¹ issued in December 2025. Under the OCS, comments are compiled in the following order: general comments are listed first, followed by comments on specific sections.

Explanatory notes on the Annex

2. The comments submitted through the OCS are hereby annexed and presented in tabulated format.
3. The concern form submitted by the USA and Canada, as presented in Appendix III of CL 2026/10-RVDF, is reproduced in this document as Annex II for convenience and consideration under agenda items 6 and 10.

¹ <https://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/>
<https://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/en/?committee=CCRVDF>

ANNEX I

COMMENT	MEMBER/OBSERVER
Canada appreciates the opportunity to provide further comments on the MRL for fumagillin dicyclohexylamine (DCH) in honey, currently at Step 6. While recognizing that parent fumagillin is not an appropriate marker residue for monitoring total fumagillin residues in honey, Canada continues to have concerns that DCH may also not be a suitable marker due to external sources of DCH in the environment that are not related to the use of fumagillin in honeybees. This concern has been further supported by a recent Canadian residue depletion study that assessed concentrations of parent fumagillin and DCH in honey samples collected from treated and untreated hives located in the province of Saskatchewan. The results of this study indicated that almost all honey samples collected from untreated hives contained detectable residues of DCH (>2.5 ng/g), with one sample containing levels that exceeded the proposed MRL of 20 µg/kg. While the study has been restricted to a single geographical area, the findings further confirm the presence of DCH in honey, which is not associated with fumagillin treatment. Thus, environmental DCH should be considered when establishing an MRL for honey. In addition to the above, the study also identified that a number of honey samples collected from treated hives contained concentrations of DCH that exceed the JECFA recommended MRL when hives were treated with fumagillin DCH in accordance with GVP (including observation of a 4-week withdrawal period). Thus, these findings indicate that the MRL, as currently proposed, is not compliant with the use of fumagillin DCH in honeybees under GVP. Given the concerns highlighted above, in addition to those identified in the joint concern form submitted by Canada and the United States of America, Canada does not support the advancement of the MRL for honey as currently proposed. However, Canada believes that should the MRL be re-assessed, a path forward utilizing DCH as the marker residue is possible. Thus, Canada commits to providing the aforementioned study and corresponding data (including the analytical methodology) to facilitate re-assessment. The concern form submitted by Canada and USA is attached as	Canada
Ecuador has not registered the active substance fumagillin dicyclohexylamine (DCH) as a veterinary drug authorized for use in its national territory for food-producing species, pursuant to official veterinary medication registries managed by the Phytosanitary and Animal Health Regulation and Control Agency and the Ministry of Agriculture and Livestock's Undersecretariat for Quality and Safety. From the perspective of risk management, the margin of exposure calculated by JECFA indicates that even in conservative scenarios, ingestion represents ≤4 % of the ADI, which demonstrates that the proposed MRLs are protective for vulnerable populations (infants and toddlers). Though fumagillin DCH is not registered in Ecuador: • Adoption of the Codex MRL is a technical reference in case residue is detected in imported products. • It provides harmonized criteria for official monitoring. • It strengthens the technical framework for any future registration requests. In that context, Ecuador believes international harmonization is preferable to a lack of any regulatory references.	Ecuador
Egypt appreciates the work done in the document and we do not object to the progress of the proposed maximum limits for residues of the veterinary drug Fumagillin dicyclohexylamine in fish and honey in the Codex Alimentarius procedures and their adoption in accordance with what was approved by the Scientific Expert Committee of JECFA, without prejudice to the position that Egypt may take in the future in the Egyptian national legislation and	Egypt

COMMENT	MEMBER/OBSERVER
food regulations it issues regarding this substance. We would also like to note the possibility of taking measures and good practices to control Nosema disease in bees without using antibiotics. The use of any antibiotics requires a risk study for the country to be in line with the policy of using antibiotics and studying antibiotic resistance.	
The European Union (EU) supports the comments made by USA and Canada in their concern form (Appendix III of CL 2026/10-RVDF). The EU recognises that JECFA has guidance on safety evaluation of residues of veterinary drugs when data packages are incomplete. It is acknowledged that, in certain scenarios, it may be possible to draw conclusions despite the absence of certain specific data. However, in this instance, we find that the available data package was excessively weak and diverged significantly from established standards. Consequently, it did not allow a comprehensive and robust assessment as would normally be anticipated.	EU
We believe the FAO/WHO Expert Committees should expand the fumagillin dicyclohexylamine (DCH) toxicology database with more scientific studies, with an emphasis on chronic effects, characterization of cumulative dietary exposure, and safety margin assessments. Given the presence of residue in frequently consumed foods, better understanding of its toxicological behaviour and associated uncertainty will make it possible to strengthen risk assessment and estimate long-term ingestion. The above will contribute to supporting a more robust scientific basis for the proposed MRLs, in line with the Codex Alimentarius principles of protecting consumer health.	Guatemala
Indonesia has not taken a stance on the submission of data for the following CL. Currently, there is no further data on the MRL for fumagillin dicyclohexylamine (DCH) residues in honey and fillets. Therefore, we will conduct further data collection regarding the DCH MRL.	Indonesia
i. Malaysia notes and generally support with the issues raised in the Canada/USA concern form, particularly those relating to data gaps in toxicology, metabolism, and residue depletion, as well as the selection of dicyclohexylamine (DCH) as a non-specific marker residue in honey. ii. Malaysia is in the view that the potential presence of DCH from environmental or industrial sources may complicate compliance verification and could lead to trade implications. Malaysia further notes that available residue depletion data in honey were not fully generated in accordance with Good Veterinary Practice (GVP), and that reported residue levels at time points relevant to honey production appear higher than the proposed MRL. Additional clarification and GVP-compliant data would strengthen confidence in the proposed MRLs. iii. For finfish, Malaysia notes the absence of residue data for DCH and limited information on the availability and validation status of analytical methods. iv. Malaysia also emphasizes the need to continue work to develop suitable and validated analytical methods capable of detecting not only fumagillin dicyclohexylamine (DCH), but also other fumagillin salts and their relevant metabolites. As fumagillin has been identified as a less stable marker compared to DCH, development of analytical methods that can simultaneously detect both fumagillin and DCH would be critical. Such methods would allow the contribution of fumagillin to the total residue definition to be appropriately considered and would future proof detection in the event of other fumagillin salt forms being used. Continuous testing is needed to address potential sources of environmental contamination despite the unknown impact of from such sources.	Malaysia

COMMENT	MEMBER/OBSERVER
v. In view of the above, Malaysia considers that additional data and clarification, as highlighted in the Canada/USA concern form, would facilitate effective risk management and implementation of the proposed MRLs. Malaysia supports continued consideration of this matter by CCRVDF and JECFA.	
Panama appreciates the research conducted by JECFA and agrees with the advancement of the MRL evaluations presented at the 98th meeting of the Joint FAO/WHO Expert Committee on Food Additives regarding the MRLs for the veterinary drug fumagillin dicyclohexylamine (DCH) in finfish (fillet) and honey; we also support the continuation of the risk assessment based on data submitted by countries that have references and scientific studies for this project.	Panama
Qatar remains committed to working collaboratively within CCRVDF to ensure that Codex standards for veterinary drug residues are science based, protective of consumer health, and supportive of fair trade.	Qatar
Senegal has no objection at this stage because these molecules are not currently used in Senegal. However, with a view to developing the beekeeping industry, professionals, while ensuring compliance with good practices in the use of antimicrobials, will be able to market products with MRLs below the draft standard.	Senegal
The United Arab Emirates (UAE) thanks JECFA for its evaluation of fumagillin dicyclohexylamine (DCH) and the establishment of the proposed MRLs for fish (fillet) and honey. After reviewing CL 2026/10-RVDF, the UAE supports a science-based approach; however, we consider that certain scientific and implementation aspects would benefit from further clarification prior to final adoption, particularly regarding honey and monitoring of DCH in fish. The UAE provides the following comments: Point Response Marker Residue in Honey The UAE notes that DCH is not a unique marker and may originate from environmental or industrial sources. Clarification is requested on whether environmental contributions were quantitatively assessed and whether alternative marker options or regulatory notes were considered to avoid enforcement and trade challenges. Additional Uncertainty Factor JECFA applied an additional uncertainty factor of 5 due to data limitations. The UAE requests clarification on the specific data gaps that led to this decision and whether additional studies are planned that may allow refinement of the ADI in future reviews. A clearer understanding of these issues will help members evaluate the strength of the toxicological assessment. Analytical Method for DCH in Fish. As a validated analytical method for DCH in fish is still to be developed, the UAE suggests that a validated method be available before the MRL is finalized, or JECFA provides guidance on interim monitoring approaches until such a method is established. Target Level for DCH in Fish Clarification is requested on whether the proposed target level (<1000 µg/kg) is supported by residue-depletion studies under approved use conditions and whether species and production system variability were considered.	UAE

COMMENT	MEMBER/OBSERVER
Dietary Exposure Assessment The estimated chronic dietary exposures (GECDEs) represent 2–4% of the ADI's upper bound, which appears acceptable. However, additional details would be helpful, particularly regarding assumptions for high consumption groups, whether honey consumption by young children was specifically evaluated, and the relative contribution of fumagillin and DCH to overall exposure.	
The UK agrees with the position put forward by the USA and Canada on the JECFA proposals for the establishment of MRLs in finfish and in honey. The evaluation was not based on the standard data requirements that JECFA would normally want to receive from a Sponsor. There is sympathy for JECFA, as the Committee managed to provide some numerical MRL recommendations to CCRVDF even though the data provided were not considered adequate for the purpose, using several risk-based approaches and increased uncertainty factors, following guidance as published in the Ninety-eighth report of the Joint FAO/WHO Expert Committee on Food Additives (WHO Technical Report Series, No. 1055). However, it is considered that this approach went further than is appropriate in this case, and the perceived conservatism introduced by using an additional safety factor (5) when calculating the ADIs for both fumagillin and DCH, to account for 'database uncertainty', may not ensure consumer safety due to the data gaps identified by USA and Canada, some of which are reiterated below. Specific areas where data absences/reductions may not be appropriately mitigated include: Toxicology: • Lack of data on metabolism and metabolites in mammalian species for both fumagillin and DCH: although the proposed MRLs are not for mammalian species, these data are required to establish whether metabolites of concern are formed in mammalian laboratory animals (for establishment of the NO(A)ELs) and/or humans. From in vitro studies (the only available studies), data indicate quite different metabolic capacities between rats and rabbits. These data were from 1968 and not well reported. • The identified fumagillin degradation products in honey were not considered to have greater toxicological concern than for fumagillin, but it is not clear on what this decision was based. • Repeat-dose, chronic toxicity studies: only one 13-week study in rats was available for review, and this used fumagillin DCH as the test item. Since residues may be expected to be consumed by humans over a lifetime in food commodities, long-term studies (1-2 years') are a key requirement for the establishment of ADIs and MRLs, in line with VICH guidance. Pragmatically, it may be possible to consider exclusion of such studies if there is a good database of shorter-term (90 days – 1 year) repeat-dose studies in more than one species, but this is not the case here. It is also noted that the NOAEL established was for fumagillin and nothing was mentioned in the report regarding the effects that might be related to the DCH moiety. • It is notable that only limited data on reproductive toxicity were available for evaluation, especially considering that effects were seen on reproductive organs in other studies. Residues: • No evaluation of metabolism of DCH in fish could be made due to lack of data. • The metabolism data for fumagillin in Rainbow Trout was not generated from a well-conducted study (tritium exchange with water far exceeded the maximum recommended in guidance), although it may be reasonable to conclude that fumagillin is not extensively metabolised in this species, as most other pharmaceutical substances are not. It would be expected that, even with the extensive tritium exchange, some trace of any metabolites would have been detected, if present.	United Kingdom

COMMENT	MEMBER/OBSERVER
• It is noted that the estimated dietary exposure for fumagillin would be less than 5% of the recommended ADI for all subpopulations of consumer; however, for DCH, no estimation was possible due to lack of data. • The UK proposes that CCRVDF should make a call for data for fumagillin DCH, to focus on gaps in the data, as identified by JECFA, USA and Canada, for both moieties. It is noted that JECFA would welcome comments from CCRVDF on the guidance used. It is therefore suggested that there should be more clarity as to what extent the guidance should be used, as it could be reasonably argued that it was relied on too heavily for this assessment. On sources of DCH in honey, the UK agrees with the concerns around potential residues of DCH originating from environmental or industrial sources, rather than veterinary use. These non-veterinary sources could trigger investigations that cannot easily identify a definitive source, which could create potential trade disruption. So, whilst the exact source of DCH does not change the potential toxicity of a residue, it is important that these potential non-veterinary residue contributions are acknowledged in any future guidance on the matter.	

ANNEX II**(Available in English only)****CONCERN FORM SUBMITTED BY CANADA AND THE UNITED STATES OF AMERICA****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 (µg/kg):** Fumagillin: 10 µg/kg in fish fillet

DCH: 20 µg/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 CCRVDF27 ⁷). 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: [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