codex alimentarius commission E

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00153 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

Agenda Item 9 **CX/RVDF 09/18/9 Add. 1**
April 2009

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Eighteenth Session

Natal, Brazil, 11-15 May 2009

DISCUSSION PAPER ON CURRENT PRACTICES AND NEEDS FOR FURTHER WORK BY THE COMMITTEE

Comments submitted by Argentina, Canada, Kenya, Iran, United States of America and IFAH (International Federation for Animal Health)

ARGENTINA

In reference to the document on risk management options, we present the following comments for each specific topic:

a) Estimated Daily Intake (EDI)

According to the recommendations of the electronic working group, the ESTIMATED DAILY INTAKE (EDI) is not an appropriate approach to determining MRLs for veterinary drug residues, and it would entail greater levels of uncertainty that would result in lower and more restrictive MRLs.

In this regard, Argentina believes that this concept should not continue to be evaluated by the Committee, and that its use should be excluded. On the other hand, Argentina supports the use of the Full Acceptable Daily Intake (Full ADI) as further explained in item (b) below.

b) Full Acceptable Daily Intake (Full ADI)

Argentina believes that the FULL ADI is the methodology that JECFA should use for the evaluation and determination of MRLs for veterinary drug residues.

However, Argentina wishes to express its concern with the concepts put forward in paragraph 26 of the document, regarding the idea that the MRLs should be set at concentrations that could monitor Good Practice in the use of Veterinary Drugs, paying attention to possible extra-label use, indirect exposure via the environment, etc.

In this regard, Argentina believes that the establishment of MRLs should not lose sight of its own objective which is to ensure food safety in order to protect the health of the consumer. The consideration of issues not related to this objective, is not only inconsistent with the basic working principles of the Codex Alimentarius, but also could result in significant problems such as:

i- the establishment of more restrictive MRLs without scientific support directly associated with the safety of food for human consumption;

ii- the rejection of imported consignments by the national authorities even though these are safe products for consumption;

iii- the potential inability of countries to use some veterinary drugs for treatments associated with husbandry practices in animals for human consumption; and

iv- losses of significant quantities of safe food products at times of high international demand for such products that could also meet the national food safety policies.

In view of this, Argentina believes that the full ADI should be used to establish MRLs. This should be done while taking into consideration the issues inherent to the drug in question or the regional habits of consumption for the food

products, and not those issues indirectly linked to safety, which could trigger restrictions in the use of certain drugs or in food trade and that are not based in safeguarding food safety.

c) Starter cultures

Argentina believes that the use of aspects associated with technical issues of the food processing industry for the establishment of MRLs for veterinary drug residues would not be justified by product safety, and that it could trigger unjustified barriers to trade.

Such aspects of technical nature associated with the cheese and yogurt industry should be addressed specifically by industry, generating the specific incentives for supplying raw material that meets the specific sought after requirements.

Argentina wishes to stress again its concern about the intention of incorporating issues not related to safety during the evaluation and recommendation of MRLs, in such a manner that these could be restrictive with respect to the use of certain veterinary drugs in professional practice and in food trade at the international level.

d) Additional Risk management Recommendations

Regarding the possibility of providing additional recommendations on risk management, in the form of footnotes, during the establishment of MRLs, Argentina believes that it is appropriate to use them as long as a REASONABLE DOUBT exists related specifically to food safety.

Similarly to our previous statement, Argentina reaffirms its concern regarding the potential incorporation of considerations linked to technological or good practice aspects that are not directly associated with safety, or with issues whose management falls under the competencies of the national authorities of each country in particular.

Specifically, Argentina would like to request that additional recommendations related to risk management should ONLY be used when clear safety issues exist that must be addressed beyond the specific MRL.

CANADA

1. **Use of the Estimated Daily Intake (EDI) concept (66th & 70th JECFA meetings)**

A. Canada agrees that the EDI approach is a more valid predictor of chronic drug residue intake than the current Theoretical Maximum Daily Intake (TMDI) approach, which is not statistically valid when applied over a lifetime of potential drug exposure. However, Canada is still concerned about implementation of the EDI approach as it currently stands. These concerns are as follows:

i. Using the median drug residue concentration in the EDI approach means that it is theoretically possible to consume drug residues that are above the acceptable daily intake (ADI), albeit intermittently and only for short periods of time. As the EDI is designed to better estimate *chronic* drug residue exposure, it does not address these short term (acute and sub-acute) higher residue concentration exposure scenarios. Although the JECFA documents imply that these short-term exposure assessments will be developed separately, possibly as an "Acute Reference Dose" (ARfD), they are not currently established. Implementation of the EDI approach is therefore not advisable until the full spectrum of complementary residue exposure scenarios is complete.

ii. Canada is concerned with the lack of detail in statistical methodology presented by JECFA in regards to the EDI approach.

   a) It is assumed that "median" values are determined by exponential regression of the residue depletion data. This is not stated explicitly however, and the actual statistical program used to perform exponential regression is not specified.

   b) As EDI is just a median value of the tissue residue concentration, its use as a benchmark to ascertain human safety does not take into account the variations observed in data due to inherent variability (e.g., variations in tissue distribution of drug between individual animals, or within individual animals at different times) as well as extraneous variability (e.g., poor experimental design/procedure or small sample size). An alternative approach to address data variability would be to use the upper 95% (or 99%) confidence interval (CI) value of the median tissue concentration to calculate the EDI. This would be something of a "hybrid" approach between the EDI and TMDI approaches: the median value, not the TMDI, is compared to the ADI (as in the EDI approach), but an upper confidence interval is applied to this number (as in the TMDI approach).

   c) In the suggested alternative EDI approach, the MRL will be determined as the upper 95th confidence interval of the 95th percentile of drug residues at the proposed withdrawal period. In this way the MRL and ADI will be determined independently ("de-linked"). However, the MRL levels are still used by the regulatory agencies to ensure food safety. This approach is inappropriate, as it "rewards" data with increased variability (such as small sample sizes or poor experimental design) with a higher MRL than data with a similar EDI but less variability. A suggestion has been earlier for using the *lower* 95% CI of 95th percentile for MRL calcula-

tion, rather than the *upper* 95% CI. An alternative could be using the lower 95% CI of 99th percentile. So long as the lower 95% CI is used, data with more variability will result in a lower MRL.

d) In simulations with real data we have found that using the lower 95% confidence interval of the 95th percentile to establish the MRL did result in lower MRLs as data variability increased. However, the difference in MRLs was negligible (generally less than 10% compared to the MRL derived from the upper 95% confidence interval). Using an upper 95% confidence interval of the median value (EDI) resulted in more significant differences. As the upper confidence of the median value is inevitably higher than the median determined by exponential regression, this approach resulted in 25 – 50% longer withdrawal periods (WPs) and correspondingly lower MRLs than simply using the median. The WPs were still shorter and MRLs higher than using the old TMDI approach however. In combination with using the lower confidence interval of the 95th percentile to calculate the MRL, this approach rewards better quality data with shorter withdrawal periods and higher MRLs.

iii. Although JECFA favours the use of the EDI approach, it acknowledges that "an adequate data set" is required to estimate the EDI. It also states that *"when data are not adequate to estimate the EDI, other conservative approaches to ensure that the ADI is not exceeded are applied"*. Before implementation of the EDI approach, a list of criteria defining an "adequate data set" is desirable so that regulatory agencies know whether to apply the EDI approach versus other conservative chronic exposure assessments (such as TMDI). This would also assist the veterinary pharmaceutical industry in designing and assessing their residue depletion trials.

B. Canada strongly supports the electronic working group's (EWG) suggestions (**para.17**) of an international workshop led by JECFA in which the EDI approach is discussed. In particular, simulations with actual residue depletion data would be most helpful in ensuring proper application of this promising approach. It would also allow experimentation with various modifications of the EDI to determine their overall effects.

2. Utilization of full ADI and Good Practices in the Use of Veterinary Drugs (GPVD)

Canada supports the recommendations outlined in **para. 27** of the EWG's discussion paper and agrees that in order to resolve the outstanding issues, JECFA may consider to revise the current definition of the MRL for veterinary drugs. In particular, Canada shares the concern of other members that GPVD could be used to "artificially" lower MRLs of veterinary drugs and thus be used as a potential trade barrier. Canada believes that MRLs should be based strictly on the human safety of incurred residues, which are universal (with the exception of differences in consumption factors between regions). However, veterinary practices vary by region as well as with time, and should not be the basis of MRL determination. Regulatory bodies can choose to apply the concept of GPVD by extending WPs for veterinary drugs.

3. Starter Cultures

Canada would agree with the EWG's recommendations (**para. 32**) provided the modified statement as follows:

> The Committee may wish to conclude on this topic by agreeing on a policy decision for the future, namely: *"When establishing a MRL for a veterinary drug* ***which has effect on starter cultures, the residues of which JECFA has evaluated and has recommended a MRL for milk,*** *on the basis of food safety consideration, the Committee shall append a risk management statement informing Codex Members that they may therefore adapt national/regional MRLs in order to address this technological aspect for trade of fresh liquid milk intended for processing using starter culture"*.

4. Appending risk management recommendation(s) to MRLs

As stated in 2) and 3), Canada is in agreement that the Good Veterinary practice or food technological aspects should not be considered when setting MRLs but have no objection on appending risk management recommendation to MRLs as footnote, as the recommendations outlined in EWG discussion paper **para. 36**.

5. Use of Regional Consumption factors

As differences in consumption factors are a major reason for the variability in MRLs, harmonization of MRLs will require some consensus of consumption factors. Canada has no objection with respect to the recommendations outlined in **para.42** of the EWG discussion paper. Canada would suggest that JECFA may co-ordinate a workshop with regulatory bodies and concerned parties to discuss this in detail.

6. Residues at Injection Sites

Canada is in support of the recommendation outlined in **para. 54** of the EWG discussion paper. Injection site residues may fall within the scope of the VICH committee evaluating studies for establishing an acute reference dose (ARfD).

7. Harmonization of Withdrawal Period Calculations

Canada agrees with the recommendation outlined in **para. 58** of the EWG discussion paper. Also, Canada supports the position that current differences in statistical calculation tools has minimal effect on the differences in resulting withdrawal periods. Other factors such as differences in MRLs, target tissue, injection site residues, implementation of

Good Animal Husbandry Practice, etc. have significantly more impact on establishing withdrawal periods. An excellent opportunity exists to harmonize statistical approaches to withdrawal period calculations during the proposed JECFA-led EDI workshop.

8. Threshold of Toxicological Concern for Veterinary Drugs

Canada is in agreement that the Threshold of Concern (TTC) appears to be a promising tool for establishing risk-based lower residue limits for substances that have no ADI/MRL (superior to the often-used approach to use analytical performance limits, such as detection/quantification limits). However, one major limitation of the approach is that, at present, no suitable TTCs for pharmacological, hormonal or microbiological effects are available; as such effects often play a considerable role in the risk assessment of veterinary drugs. The TTC concept is in need of further development and extension/validation before it could be used in the assessment of pharmacologically active substances. Canada is in support of the position that these issues should be discussed further.

KENYA

Background

When finalizing its document on Risk Management Methodologies, including Risk Assessment Policies, during its 16th session, the Codex Committee on Residues of Veterinary Drugs in Foods acknowledged that there was a need for further discussion related to risk management options including risk assessment policy (ALINORM 06/29/31, para. 112-114). The 16th session of the Committee also agreed to establish an electronic Working Group, led by France, to prepare a Discussion Paper to identify risk management topics and options to be considered at its next session.

H.- Residues at injection sites

The 17th session of the Committee "also agreed that proposal (C-3) "Residues at injection sites" be taken up for consideration in the future taking account of the estimation of acute reference doses published by JMPR, the work on the same topic planned by JECFA and the consideration planned by VICH, when they become available." (see ALINORM 08/31/26 – para. 131) old drug policy. It noted however that, as these old drugs had no patent protection, it was unlikely that a sponsor would undertake the expense to submit the appropriate data to JECFA/Codex.

The in-session Working Group, held during the 17th session of the Committee, had classified the proposals listed in document CX/RVDF 07/17/13 into four mains categories:

1. Topics that should be taken up immediately for consideration by the Committee

2. Topics that the Committee should address in the future

3. Topics for which no further work was required

4. Topics for which further clarification should be provided at the next session of the Committee:

Comments

*We proposes that **'(C-3)Residues at injection sites'** which falls under topic 2 that needs to be addressed in the future, needs to be elevated to the 'topics that should be taken up immediately for consideration by the committee.*

We have noted that it is a critical food-safety issue and a major concern in meat hygiene industries.

IRAN

A-Use of the Estimated Daily Intake (EDI)concepts

Iran believes the EDI approach is still source of concerns and we aren't agreed with use of EDI

B-Utilization of full ADI:

Iran isn't agreed with use of ADI. Although use of full ADI is scientifically justifiable within the current bases for Risk assessment, however due to the possible extra-label use of veterinary drugs and possible uses in minor species, it is recommended not to use full ADI to provide an extra safety margin.

C-Starter cultures:

Iran supports the recommendation to consider of food technology aspects in the establishment of a MRL.So ,Codex Members may adapt national/regional MRLs in order to address this technological aspects for trade of fresh milk intended for processing using starter culture.

D-Appending risk management recommendations to MRLs

Iran is agreed with appending risk management recommendations to MRLs .This recommendations would assist risk managers and provide guidance on Good Veterinary Practice (GVP)

E-Use of Regional Consumption Factors

Iran is agreed with postponing consideration of this issue due to lack of adequate data about use of regional consumption factors.

F-Old Drug Policy

Iran has no specific comment to offer at "Old Drug Policy". We believe this item is vague and needs more clarification.

G-Threshold of Toxicological Concern for Veterinary Drugs

Iran is agreed to discuss this item further. We are in opinion that the threshold of toxicological concern (TTC) of veterinary drugs needs to be further developed and validated.

H-Residue at injection sites

Iran is agreed to wait for the on-going work by VICH before taking up this matter again.

I-Harmonization of withdrawal period's calculation

Iran supports the recommendation to wait for the conclusion of the on-going work by VICH before taking up this matter again.

UNITED STATES OF AMERICA

The United States would like to bring forward a topic needing urgent discussion by the Risk Management Working Group prior to or during the 18th Session of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) in Natal, Brazil.

With the decision by the WTO to rely on Codex standards as a basis for safety to consumers and fair trade practices the potential for trade barriers has increased as Maximum Residue Limits for Veterinary Drugs (MRLVDs) are established to reflect the veterinary practices occurring at the time of the JECFA evaluation.

The current interpretations of the definition of the MRLVD place unwarranted emphasis on residue concentrations that reflect approved label uses at a specific point in time rather than concentrations that reflect the safety of residues. For certain veterinary drugs, this has led to the establishment of MRLVDs that are significantly below those concentrations determined to be safe for human consumption (i.e., these residue concentrations do not result in exceeding the acceptable daily intake). This difference between the upper bound of concentrations that may be safe for human consumption, and the concentration that may be safe and reflect certain approved drug uses can result in significant trade problems.

These include:

- commodities in international trade rejected for import by national authorities despite being safe for consumption;
- the inability of countries, particularly developing countries, to use veterinary drugs for important disease intervention and production uses in food-producing animals;
- significant costs for highly sensitive analytical methods; and
- losses of significant quantities of safe, nutritious food

The Procedure Manual clearly states that the Codex Alimentarius is a collection of internationally adopted food standards and related texts aimed at protecting consumer health and ensuring fair practices in the international food trade. In order for the CCRVDF to fulfill its terms of reference and remain aligned with the principles of the Codex Alimentarius, the Committee should re-evaluate the current interpretation of the definition of the MRLVD. The definition of a MRLVD is provided on page 43 of the 17th edition of the Codex Alimentarius Commission Procedure Manual.

MRLVDs adopted by the Codex Alimentarius Commission have been through years of development from a thorough JECFA evaluation and the multi-year Codex step process. While it is possible to propose a re-evaluation of an existing MRLVD, the time and expense necessary to change or update the MRLVD to reflect a new veterinary drug use or dosage regimen is often impractical. Adopted MRLVDs become essentially timeless and enduring. Codex MRLVDs are established on the basis of current veterinary practice in a particular country or region at the time of the JEFCA evaluation. As veterinary medical science progresses, new uses for existing veterinary drugs are discovered and dosage regimens of veterinary drugs are changed to reflect current therapeutic and production needs. Consequently, the MRLVDs may not be reflective of newer therapeutic and production needs and thus may obstruct progress in veterinary medicine.

Therefore, to assure adopted MRLVDs are durable and adequately address the objectives of Codex, they must reflect the safety of the incurred residues and not reflect a particular legal use that existed at the time of the evaluation. The MRLVD should reflect the maximum concentration of residues that have been shown to be safe for human consumption. Accordingly, the recommended MRLVDs must fully reflect the ADI established by the JECFA. This approach

will protect human health and enable fair trade of commodities derived from treated animals based on the scientific evaluation of the safety of those residues.

An important part of this issue rests with how a portion of the MRLVD definition is currently being interpreted. The current interpretation of the phrase "the MRLVD may be reduced to be consistent with good practices in the use of veterinary drugs" has been an implied requirement for establishing an MRLVD based on the indications and conditions of use at the time of the evaluation. This interpretation incorporates no regard for the potential for new and changing uses of the veterinary drug or for specific conditions existing in and perhaps limited to developing countries.

While it is important that the residue data submitted in support of an MRLVD be the result of studies conducted in compliance with good practice in the use of veterinary drugs (GPVD), it is proposed that residues resulting from approved label use not be the basis for the derivation of the MRLVDs. Rather, a total residues approach is proposed where the concentration of total residues in a each edible tissue is determined based on the ADI and the fraction of the total diet represented by that edible tissue. The MRLVD would then represent the concentration of a marker residue in a specific tissue that reflects the concentration of total residues in that tissue the consumption of which would not exceed the ADI based on the total residues in that tissue.

The resulting MRLVD would represent an upper bound of residues in the edible tissues that is safe for chronic human consumption and would not result in exceeding the ADI. Because the MRLVDs would not be limited to a specific treatment regimen, they would be applicable to a wide range of doses and treatments and, when novel treatment regimens or evolving disease conditions benefiting from the use of a specific drug are identified, the MRLVDs would remain applicable. It would remain the purview of the regional and national regulatory authorities to assure that the use of the veterinary drug was in accordance with GPVD.

We recommend that this concept be brought forward in the Risk Management Working Group for discussion before or during the 18th Session of the CCRVDF.

IFAH (International Federation for Animal Health)

The International Federation for Animal Health (IFAH) appreciates the opportunity to comment on this important topic of risk management and the role of CCRVDF in establishing MRLs (Maximum Residue Levels) for residues of veterinary drugs in foods. IFAH would also like to commend the French Delegation for organizing the comments from the members, establishing priorities and providing recommendations for the Committee to discuss.

IFAH's comments on each of the recommendations will be identified by the corresponding paragraph number.

Paragraph 17 & 27 – IFAH believes that the Estimated Daily Intake (EDI) approach represents a more realistic estimate of exposure to residues of veterinary drugs; however, the EDI approach is still unnecessarily conservative. CCRVDF needs to reconsider the definition of a residue of a veterinary drug to permit full utilization of the ADI. The MRLs should not be determined by "use patterns" based on Good Veterinary Practices but by toxicology. If CCRVDF can agree to reconsider the definition (or the interpretation) of the definition of a veterinary drug, IFAH would support JECFA coordinating a workshop to review various procedures for calculating MRLs using the full ADI. The adoption of a policy to utilize the full ADI would have benefits that would impact many additional areas/issues now being debated within JECFA and CCRVDF.

Trade

Although JECFA and CCRVDF have been focused on meeting their first objective of setting food-safety standards (MRLs), because of the conservative nature of these standards Codex may not be adequately addressing the second objective of facilitating international trade. The use of the full ADI in setting safe but more realistic MRLs would significantly improve the ability of JECFA/CCRVDF to meet this second objective without compromising consumer safety.

The frequency of violative residues in edible commodities detected by national or international surveillance programs would be reduced. This is a natural consequence of full use of the ADI and potentially higher (but still safe) MRLs. The assertion that MRLs are necessary to ensure Good Veterinary Practices is reverse logic. The encouragement of the application of GVPs by producers, regulators and pharmaceutical companies will necessarily result in residues far below the MRL when this standard is based on food safety. Hence, the potential for residue violations will be decreased.

Surveillance programs are expensive from the perspectives of direct out-of-pocket costs, personnel requirements and time investment. The question must be asked as to why JECFA/CCRVDF would want to implement food standard policies that may result in detection of "violative residues" in food that is truly safe for consumption.

Estimated Daily Intake

The new JECFA policy to assess residue consumption with respect to the Estimated Daily Intake (EDI) instead of using the Total Maximum Daily Intake (TMDI) has resulted in substantial debate and comment at the 17th CCRVDF as well as in recent documents.

It is proposed that recognition of the MRL solely as a food-safety standard with a direct mathematical relationship to the ADI, would eliminate the need for further consideration of the EDI concept. The EDI calculation only becomes necessary when MRLs are established at arbitrary points along a residue depletion curve consistent with JECFA's current assumptions of GVPs. As the potential actions under consideration by the Risk Management Group are numerous with respect to this area, substantial resources could be re-focused to other CCRVDF issues if the EDI was no longer relevant.

Injection Sites

Use of the full ADI and target tissue approach would not resolve, but would substantially improve the management of injection site issues. Full use of the ADI would potentially allow increased (and safe) MRLs for muscle, which may result in decreased withdrawal times in regions where the same MRL is applied to injection site muscle as it is to distant muscle for residue testing.

A secondary benefit related to surveillance would also be realized. One of the impediments for adoption of the dual-sampling proposal for monitoring potential injection site residues is the requirement for additional personnel for sampling and subsequent assay of the "second" sample. Adoption of a target-tissue approach would reduce the need to monitor all edible tissues and thus resources would become available for other assignments. As such, implementation of a second sample approach would be possible without any increased resource costs.

Codex MRLs in advance of first registration

The US Delegation has submitted a proposal through the priorities working group to allow submission of a dossier for JECFA evaluation in advance of approval/registration by a national authority. Implementation of this proposal would be considerably easier with concurrent implementation of use of the full ADI. One of the recognized issues with respect to early JECFA evaluation is the degree of data availability from the sponsor. Under the current system, JECFA requests a full dossier including all toxicology data, total residue, metabolism and marker residue studies along with a validated analytical method. This would change under a system where the MRL could be directly derived from the ADI. The sponsor would still need to submit the toxicology package (for the ADI) but only a total residue study and a metabolism study (which determined the marker residue and marker residue ratio) would be required. [Note: evaluation of an MRL does not require a marker residue depletion study]. Such a policy change would allow Sponsors to submit data much earlier for evaluation, which, would result in a substantially earlier MRL decisions. The availability of an international food safety standard would clearly remove barriers to international trade when the product finally achieves its initial registration(s).

Impact on analytical methods

Linking the calculation of the MRL directly to the ADI has considerable advantages from the perspective of analytical methods. Following conduct of the total residue and metabolism study, where the marker residue is identified, the Sponsor can calculate an approximate MRL. Analytical methods can then be developed and validated relative to that MRL. This represents a substantially improved procedure and removes the uncertainty and arbitrary nature of how JECFA currently elaborates MRLs following consideration of Good Veterinary Practices.

Use of the full ADI with the resulting potential increase in MRLs (which still represent safe levels for human consumption) would reduce the need for overly sensitive analytical methods. This would positively impact surveillance programs, especially in developing countries, as the need to invest in the most sensitive equipment may be reduced.

Paragraph 32 & 36 – IFAH supports these recommendations: (1) MRLs should be based on food safety and not on the effects on starter cultures, and (2) the appending of risk management recommendations to MRLs.

Paragraph 42 – This recommendation should be discussed in the context of using the full ADI. IFAH does not support using regional consumption factors. With regional consumption factors, there would be no harmonization of MRLs; therefore, regional consumption factors do not accomplish the primary activity of Codex. IFAH does not support sending this recommendation to JECFA. This topic is an integral part of any Risk Management Policy and should be determined by the Risk Managers, CCRVDF.

Paragraph 50 – IFAH supports this recommendation and supports JECFA's activities on developing a Threshold of Concern (TTC) for veterinary drugs.

Paragraph 54 & 58 – IFAH supports these recommendations. OIE will report on the activities of VICH at the 18th Session of CCRVDF.