CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 3 **CF11/CRD03**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON CONTAMINANTS IN FOODS

Eleventh Session
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REPORT OF THE IN-SESSION WORKING GROUP ON THE FOLLOW UP TO THE OUTCOME OF THE 83rd MEETING OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA), ROME, 8-17 NOVEMBER 2016

I. INTRODUCTION

The in-session working group (WG) was held on 4 April 2017 and chaired by Mr. Frans Verstraete (EU). Dr. Vittorio Fattori and Dr. Markus Lipp (both FAO/JECFA Secretariat) and Dr. Angelika Tritscher (WHO/JECFA Secretariat) assisted the Chair.

II. 83rd MEETING OF JECFA (JECFA83)

JECFA83 addressed the following contaminants: aflatoxin, diacetoxyscirpenol, fumonisins, glycidyl esters, 3-MCPD esters, sterigmatocystin and co-exposure of aflatoxins and fumonisins. The summary report of the 83rd JECFA meeting is attached as Annex to CX/CF 17/11/3. The report of the meeting is published: Evaluation of certain contaminants in food (Eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, 1002, 2017 available at http://apps.who.int/iris/bitstream/10665/254893/1/9789241210027-eng.pdf?ua=1.

II.A AFLATOXINS

Conclusions and recommendations by JECFA (not exhaustive)

The Committee reaffirmed the conclusions of the forty-ninth meeting of JECFA that aflatoxins are among the most potent mutagenic and carcinogenic substances known, based on studies in test species and human epidemiological studies, and that hepatitis B virus (HBV) infection is a critical contributor to the potency of aflatoxins in inducing liver cancer.

The Committee concluded that enforcing an ML of 10, 8 or 4 µg/kg for ready-to-eat peanuts would have little further impact on dietary exposure to AFT for the general population, compared with setting an ML of 15 µg/kg. At an ML of 4 µg/kg, the proportion of the world market of ready-to-eat peanuts rejected would be approximately double the proportion rejected at an ML of 15 µg/kg (about 20% versus 10%).

The Committee recommends that efforts continue to reduce aflatoxin exposure using valid intervention strategies, including the development of effective, sustainable and universally applicable pre-harvest prevention strategies.

Based on their contribution to dietary aflatoxin exposure in some areas of the world, rice, wheat and sorghum need to be considered in future risk management activities for aflatoxins.

The Committee recommends further research and efforts to alleviate stunting taking aflatoxin exposure into consideration as a possible contributing factor.

The Committee recommends that if additional epidemiological studies are conducted, they should be prospective studies and performed in a high exposure area (e.g. in Africa).

The Committee advises the development of surveillance programmes for regions for which currently little information on occurrence of aflatoxins exists, carefully considering the impact of these programmes on food security.

Discussion on follow-up action

As regards the presence of aflatoxins in ready-to-eat peanuts, the follow up is discussed under agenda item 11 at this meeting of CCCF.

Reference was made to the "Code of Practice for the Prevention and Reduction of Mycotoxin Contamination in Cereals (CAC/RCP 51-2003

As regards the recommendation by JECFA, that based on their contribution to dietary aflatoxin exposure in some areas of the world, rice, wheat and sorghum would need to be considered in future risk management activities for aflatoxins, reference was made to the discussions that has taken place at the 8th Session of CCCF in 2014: "*103. The Committee agreed that countries would submit data to GEMS/Food and no further work would be undertaken on the establishment of MLs for aflatoxins in cereals for the time being."*

The WG was of the opinion that it would be appropriate to reconsider this conclusion taking into account the outcome of the assessment performed and recommendations by JECFA. It is therefore appropriate that a discussion paper is prepared to enable the CCCF to take at CCCF12 an informed decision on the appropriate follow-up action.

II.B 4,15 DIACETOXYSCIRPENOL (DAS)

Conclusions and recommendations by JECFA (not exhaustive)

4,15-DAS and T-2/HT-2 toxin are structurally similar, and there is evidence that they cause similar effects at the biochemical and cellular levels, have similarities in toxic effects in vivo and have an additive dose effect when co-exposure occurs. Therefore, the evidence was considered sufficient by the Committee to support including 4,15-DAS in the group provisional maximum tolerable daily intake (PMTDI) for T-2 and HT-2 toxin established at the forty-seventh JECFA meeting. The PMTDI of 0.06 µg/kg bw for T-2 and HT-2 toxin, alone or in combination, was established based on a lowest-observed-adverse-effect level (LOAEL) of 0.03 mg/kg bw per day associated with changes in white blood cell counts following 3 weeks of dietary exposure in pigs and the application of an uncertainty factor of 500. The inclusion of 4,15-DAS in the group PMTDI of 0.06 µg/kg bw is considered to be a conservative approach when taking into consideration the observation that T-2 toxin was consistently more potent than 4,15-DAS when comparing similar in vitro and in vivo end-points.

The Committee noted that there is a paucity of occurrence data and what data were available to the Committee frequently were left censored, thereby increasing the uncertainty in the exposure assessment.

The Committee was made aware of new toxicity studies on T-2/HT-2 toxin and therefore recommends an update of the 2001 JECFA evaluation of T-2/HT-2 toxin. In addition, studies are needed to address the relative potencies of 4,15- DAS and T-2/HT-2 toxin, the species differences with regard to bioavailability following oral exposure, the potential for chronic toxicity from exposure to concentrations in the diet, and the potential for reproductive and developmental toxicity of 4,15-DAS.

The Committee recommends improving the LOQs for 4,15-DAS, particularly when developing multi-mycotoxin methods. The Committee encourages the development of analytical standards, suitable certified reference materials and proficiency tests to support the analysis of 4,15-DAS and its modified forms, including biomarkers.

The Committee recommends that more food commodities be analysed using methods with appropriate sensitivity that would allow the refinement of its estimates of dietary exposure to DAS, T-2 and HT-2 from all regions.

Discussion on follow-up action

The WG agreed that it is appropriate to request JECFA update the 2001 JECFA evaluation of T-2/HT-2 toxin taking into account new toxicity studies. Furthermore the exposure assessment should be based upon more recent occurrence data on the presence of T-2 and HT-2 toxin and 4,15 DAS in food. Member countries are requested to provide recent occurrence data on the presence of T-2, HT-2 toxin and 4,15 DAS to the GEMS/Food contaminants database. For the generation of these occurrence data it is necessary to use methods of analysis with appropriate sensitivity.

II.C FUMONISINS (FB1, FB2 and FB3)

Conclusions and recommendations by JECFA (not exhaustive)

Fumonisins were evaluated by the present Committee in response to a request from CCCF for an updated exposure assessment. The Committee also evaluated toxicological and epidemiological studies that had become available since the previous evaluation in 2011.

The previously established group PMTDI of 2 µg/kg bw for FB1, FB2 and FB3, alone or in combination, was retained by the current Committee.

The Committee noted the paucity of new data on the occurrence of fumonisins in food submitted to the GEMS/Food contaminants database since 2011 by all WHO regions except for Europe, as opposed to the data used in the previous evaluation (2011). Owing to these differences in the data sets between 2011 and the current evaluation, a direct comparison was not possible.

The Committee noted that the international exposure estimates for FB1 and total fumonisins were lower than those estimated by the Committee at its seventy-fourth meeting in 2011. In the current assessment, a larger part of the occurrence data was from countries belonging to the WHO European Region compared with 2011, resulting in lower overall fumonisin levels in maize. In the current assessment, no information on fumonisin levels in maize was available from countries belonging to the African, Eastern Mediterranean or South-East Asia regions, where higher fumonisin concentrations are typically detected.

Given these limitations of the occurrence data used in the exposure assessment and high exposures reported in the literature in some countries, it is likely that the exposures to fumonisins in areas where maize is a staple food and high contamination with fumonisins can occur are higher than those estimated by the Committee at this meeting, as can be seen in the previous evaluation, which was based on a larger and more representative data set.

The Committee noted the need for data on FB1 in breast milk using analytical methods with appropriate specificity and sensitivity in order to further evaluate this potential exposure route.

The Committee recommended that exposure to fumonisins be reduced, particularly in areas where maize is the major dietary staple food and where high contamination can occur.

The Committee advises the development of surveillance programmes for regions for which little current information on occurrence of fumonisins in the GEMS/Food contaminants database exists, carefully considering the impact of these programmes on food security. The Committee recommended that these countries be encouraged to submit fumonisin concentration data to the GEMS/Food contaminants database. The Committee recommended that countries be encouraged to analyse fumonisins in food samples using analytical methods with appropriate sensitivity to reduce the uncertainty in the exposure assessment, especially for maize and wheat.

The Committee recommends that additional studies be conducted to better understand the occurrence of bound fumonisins in different cereals, the impact of processing on these bound mycotoxins and their bioavailability after consumption.

Discussion on follow-up action

Reference was made to the discussions that has taken place and the conclusions agreed at the 8th Session of CCCF in 2014: "*71. Noting that there were no outstanding issues on the MLs and sampling plans, the Committee agreed that the ML of 4 000 µg/kg for raw cereal grains and 2 000 µg/kg for maize flour and maize meal were ready for adoption by the Commission. In relation to the ML for maize flour and maize meal, the Committee agreed that these would be advanced for adoption with the understanding that exposure and impact assessment should be undertaken by JECFA within three years for reconsideration of the levels*."

The JECFA representative regretted that in the light of the discussions at the 8th Session and the conclusions made as referred above that no new information on fumonisin levels in maize was made available for this assessment from countries belonging to the African, Eastern Mediterranean or South-East Asia regions, where higher fumonisin concentrations are typically detected.

It was agreed by the WG that no action is to be undertaken by CCCF following this assessment. A strong call to countries belonging to the African, Eastern Mediterranean or South-East Asia regions to provide

to GEMS/Food contaminants database as yet information on fumonisin levels in maize should be made and recorded in the report of the meeting.

II.E GLYCIDYL ESTERS, 3-MCPD esters and 3-MCPD

Conclusions and recommendations by JECFA (not exhaustive)

Glycidyl esters

Glycidyl esters are processing-induced contaminants primarily found in refined fats and oils and foods containing fats and oils. Experimental evidence indicates that glycidyl esters are substantially hydrolysed to glycidol in the gastrointestinal tract and elicit toxicity as glycidol.

The Committee concluded that glycidol is a genotoxic compound and considered its carcinogenicity as the most sensitive end-point on which to base a point of departure (lowest BMDL10 is 2.4 mg/kg bw per day).

As it is not appropriate to establish a health-based guidance value for substances that are both genotoxic and carcinogenic, the margin of exposure approach is chosen. The Committee considered that the lower ends of the ranges of the margins of exposure for infants, children and adults were low for a compound that is genotoxic and carcinogenic and that they may indicate a human health concern.

The Committee recommends that appropriate efforts to reduce concentrations of glycidyl esters and glycidol in fats and oils, in particular when used in infant formula, should continue to be implemented.

The Committee recommends the development of better exposure biomarkers to facilitate measurements in humans consuming glycidyl esters in food in support of risk assessment.

The Committee recommends that additional international collaborative studies should be undertaken on methods of analysis for glycidyl esters in relevant fat- or oil-containing foods in order to remove the uncertainty surrounding the accuracy of the data submitted to the GEMS/Food contaminants database used in future evaluations.

It is recommended that more data be submitted to the GEMS/Food contaminants database, including the form (the ester form or not) and the analytical methods used, in particular for fats and poils, where a high degree of variability in concentration is observed.

3-Monochloro-1,2-propanediol (3-MCPD) esters

3-Monochloro-1,2-propanediol (3-MCPD) esters are processing-induced contaminants found in various refined oils and fats and are formed from acylglycerols in the presence of chlorinated compounds during deodorization at high temperature.

No genotoxic potential has been demonstrated in vivo for 3-MCPD. Two long-term carcinogenicity studies with 3-MCPD in rats5 were identified as pivotal studies, and renal tubular hyperplasia was identified as the most sensitive end-point. The lowest BMDL10 (restricted log-logistic model) for renal tubular hyperplasia was calculated to be 0.87 mg/kg bw per day for male rats. After application of a 200-fold uncertainty factor, the Committee established a group PMTDI of 4 µg/kg bw for 3-MCPD and 3-MCPD esters singly or in combination (expressed as 3-MCPD equivalents) (rounded to one significant figure). The overall uncertainty factor of 200 incorporates a factor of 2 related to the inadequacies in the studies of reproductive toxicity.

The Committee noted that estimated dietary exposures to 3-MCPD for the general population, even for high consumers (up to 3.8 µg/kg bw per day), did not exceed the new PMTDI. Estimates of mean dietary exposure to 3-MCPD for formula-fed infants, however, could exceed the PMTDI by up to 2.5-fold for certain countries (e.g. 10 µg/kg bw per day in the first month of life).

The Committee recommends that appropriate efforts to reduce concentrations of 3-MCPD esters and 3-MCPD in infant formula continue to be implemented.

The Committee recommends that additional international collaborative studies should be undertaken on methods of analysis for 3-MCPD esters in relevant fat- or oil-containing foods in order to remove the uncertainty surrounding the accuracy of the data submitted to the GEMS/Food contaminants database for use in future evaluations.

To address the uncertainty associated with reproductive effects, experimental studies would be required to elucidate the potential reproductive toxicity of 3-MCPD esters, including exposure of newborns.

Discussion on follow-up action

Reference was made to the proposal submitted by the USA for new work on a Code of Practice for the Reduction of 3-monochloropropane-1,2-diol esters and glycidyl esters in refined oils and products made with refined oils, especially infant formula, available as CRD 10.

A delegation made the comment that it might be premature to start new work on a Code of Practice as studies are still ongoing on mitigation measures to reduce the presence of glycidyl and 3-MCPD esters in refined vegetable oils.

The USA referred to the timeline for completion of the work as provided for in the draft project document and indicated that the work is not expected to be finalised before 2019/2020 and therefore there will be the possibility to take into account the outcome of these studies into the Code of Practice.

Following this exchange of views, the WG agreed to support the abovementioned proposal submitted by the USA for new work.

II.F STERIGMATOCYSTIN

Conclusions and recommendations by JECFA (not exhaustive)

Structurally, sterigmatocystin is closely related to aflatoxins. Sterigmatocystin is an intermediate in the biosynthetic pathway for aflatoxins. *Aspergillus versicolor* and *A. nidulans* do not contain the enzymes necessary for the conversion of sterigmatocystin into aflatoxin.

Taking account of the available information on genotoxicity, carcinogenicity and DNA adduct formation, the Committee concluded that sterigmatocystin is genotoxic and carcinogenic, and the critical effect was determined to be carcinogenicity. The Committee selected the BMDL10 of 0.16 mg/kg bw per day as the point of departure for use in the risk assessment.

As it is not appropriate to establish a health-based guidance value for substances that are genotoxic carcinogens, the Committee used a margin of exposure approach. The Committee noted that there is a paucity of occurrence data and what data were available to the Committee frequently were left censored, thereby increasing the uncertainty in the exposure assessment.

The Committee noted that the calculated margins of exposure, which are based only on adult populations and for which only one food commodity (sorghum) was considered, may indicate a human health concern. Margins of exposure were not calculated for Europe or Japan, as sterigmatocystin was not detected in any samples. For all other regions, the Committee considered that the margins of exposure were not of human health concern.

The Committee also noted that sterigmatocystin and AFB1 have the same main target organ (the liver). The comparative animal data on carcinogenicity are very limited, but indicate that sterigmatocystin is less potent than AFB1.

The Committee recommends improving the LOQs for sterigmatocystin, particularly when developing multi-mycotoxin methods. The Committee recommends that more food commodities, especially stored crops, be analysed with appropriate analytical LODs that would allow refining the estimates of dietary exposure to sterigmatocystin from all regions.

The Committee encourages the development of suitable certified reference materials and proficiency tests to support the analysis of sterigmatocystin.

Discussion on follow-up action

Given that JECFA has concluded that the calculated margins of exposure, which are based only on adult populations and for which only one food commodity (sorghum) was considered, may indicate a human health concern, the WG agreed that the discussion paper on aflatoxins in cereals (see point II.A) to be prepared to enable the CCCF to take at CCCF12 an informed decision on the appropriate follow-up should also include sterigmatocystin in cereals also in view of enabling the CCCF to take at CCCF-12 an informed decision on the appropriate follow-up.

II.G CO-EXPOSURE OF FUMONINS WITH AFLATOXINS

Conclusions and recommendations by JECFA (not exhaustive)

The Committee concluded that there are few data available to support co-exposure as a contributing factor in human disease. However, the interaction between AFB1, a compound with known genotoxic properties, and fumonisins, which have the potential to induce regenerative cell proliferation (particularly at exposures above the PMTDI), remains a concern. This is due to the fact that the incidences of chronic liver disease and stunting are high in the areas of the world where the exposures to both mycotoxins are high and the co-exposure has been confirmed with biomarkers.

There is a need to reduce human exposure to aflatoxins and fumonisins, alone or in combination, in particular in developing countries.With regards to human studies, the emphasis should be on biomarker-based approaches. Biomarker-based studies in high-risk areas should include attempts to characterize the health issues common in individuals within communities where exposure is high, which can be compared with similar communities where exposure is low.

Experimental animal feeding studies should also use biomarker-based approaches and should be designed with multiple dose levels that reflect the levels of contamination seen in areas at high risk for co-exposure.

Discussion on follow-up action

No specific follow-up action to be recommended to the CCCF was identified.

III. PYRROLIZIDINE ALKALOIDS (PAs)

Reference is made to the information note made to the agenda of this meeting of CCCF:*"Work on PAs will be considered as a follow up to the JECFA evaluation (REP16/CF, paragraph 173)."*

The JECFA representative indicated that the monograph on PAs is not yet published but committed that the publication shall be done before the 12th session of CCCF in 2018

IV. RECOMMENDATIONS TO CCCF FOR FOLLOW-UP ACTIONS

The WG agreed to put forward to the CCCF for consideration following recommendations for follow-up actions following the outcome of JECFA83:

a) to agree that **a discussion paper is prepared on aflatoxins and sterigmatocystin in cereals** (in particular maize, rice, sorghum and wheat) to enable the CCCF to take at CCCF12 an informed decision on the appropriate follow-up as regards possible risk management options for aflatoxins and sterigmatocystin in cereals

b) to agree **to request JECFA to update the 2001 JECFA evaluation of T-2/HT-2 toxin** taking into account new toxicity studies (i.e. inclusion in the priority list). Furthermore the exposure assessment should be based upon more recent occurrence data on the presence of T-2 and HT-2 toxin and 4,15 Diacetoxyscirpenol (DAS) in food. Member countries are requested to provide recent occurrence data on the presence of T-2, HT-2 toxin and 4,15 DAS to the GEMS/Food contaminants database. For the generation of these occurrence data it is necessary to use methods of analysis with appropriate sensitivity.

c) to make **a call to countries** belonging to the African, Eastern Mediterranean or South-East Asia regions **to provide to GEMS/Food contaminants database** as yet information on **fumonisin levels in maize** and to record this in the report of the meeting.

d) to agree to submit **new work** for adoption by CAC on **a Code of Practice for the Reduction of 3-monochloropropane-1,2-diol esters and glycidyl esters in refined oils and products made with refined oils, especially infant formula** (project document available in CRD 10)