A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held on a virtual online platform from 24 March to 1 April 2022. The purpose of the meeting was to evaluate the safety of certain food contaminants, specifically the trichothecenes T-2, HT-2 and 4,15-diacetoxyscirpenol (DAS). The exposure assessment and the chemical characterization had already been carried out at the ninetieth meeting of the Committee. Therefore, the purpose of this meeting was to review the toxicological data on the trichothecenes T-2, HT-2 and DAS and conduct a safety evaluation and a re-evaluation of the combined dietary exposure. The present meeting was the ninety-third in a series of similar meetings.

Because of the travel restrictions and lockdowns due to the COVID-19 pandemic in many countries, it was not possible for the joint FAO/WHO JECFA secretariat to convene an in-person meeting. Therefore, the meeting was held as a videoconference. In view of the time differences in the countries of origin of the invited experts, the only possible time for a videoconference was restricted to a 3-hour time slot (12:00–15:00 CEST) each day.

Dr. D.J. Benford served as Chairperson.

Dr. U. Mueller served as Rapporteur.

The full toxicological evaluation and overall risk characterization of the trichothecenes T-2 and HT-2 was originally scheduled for the ninetieth meeting of JECFA, which was held in 2020. However, it became apparent during that meeting that there was insufficient time for the evaluation, and it was agreed to schedule it for a future meeting.

The report of the meeting will be published in the WHO Technical Report Series. The report will summarize the main conclusions of the Committee regarding the group acute reference dose (ARfD) and tolerable daily intake (TDI) for T-2, HT-2 and DAS, as well as the risk characterization and recommendations. Its presentation will be similar to that of previous reports. An annex will include a summary (similar to the summary in this report) of the main conclusions of the Committee’s toxicological and safety recommendations.

The participants are listed in Annex 1 to this summary document. Future work and recommendations arising from the meeting are summarized in Annex 2. Annex 3 summarizes observations by experts with regard to the practicability of holding these expert meetings online rather than in-person.

Toxicological and dietary exposure monographs on the contaminants considered will be published in FAS 84.

More information on the work of JECFA is available at:

and
https://www.who.int/foodsafety/en/

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Toxicological and dietary exposure information and conclusions

Contaminants evaluated

Review of toxicological data on the trichothecenes T-2, HT-2 and DAS and re-evaluation of the combined dietary exposure

At its ninetieth meeting, JECFA reviewed the information that had become available after the fifty-sixth meeting on T-2 and HT-2 concerning analytical methods, sampling, effect of processing, prevention and control, occurrence in food commodities and dietary exposure. The toxicological data were addressed at the current meeting and the combined dietary exposure was re-evaluated.

Following acute and short-term intake in multiple species, T-2 exposure induces emesis, reduced feed intake, reduced body weight gain, immunotoxicity and haematotoxicity. No suitable long-term studies were identified for establishing a tolerable intake for T-2 and HT-2. Nonetheless, based on the critical effects seen in several acute and short-term studies, the Committee concluded that the safety of food contaminated with T-2 or HT-2 could be evaluated.

Furthermore, as previously recommended, the current Committee considered the issue of additivity with respect to DAS exposure. In particular, the current Committee noted that additivity is supported by more recent acute toxicity data indicating that DAS exhibits similar emetic effects in mink via a similar mode of action to T-2 and HT-2, but at a lower relative potency. Additionally, there is limited evidence that DAS can be detected as a co-contaminant with T-2 and HT-2, particularly where analytical methods with low limits of detection (LODs) are used.

Although the effects and proposed mechanisms elicited by other trichothecenes appear similar, the current Committee concluded that, with the exception of DAS, the evidence for grouping other trichothecenes or establishing relative potency factors, was inadequate and beyond the scope of this addendum.

Group acute reference dose (ARfD)

Emesis is a common effect of acute trichothecene exposure in both humans and experimental animals. On this basis, the Committee established a group ARfD for T-2, HT-2 and DAS using the lower 95% confidence limit on the benchmark dose for a 10% response (BMDL10) of 2.6 µg/kg bw for emesis in mink following acute gavage exposure to T-2 or HT-2 as the point of departure. Based on the available evidence, the Committee decided that an uncertainty factor of 8 (2.5 for interspecies variability in toxicodynamics and 3.16 for intra-human variability in toxicodynamics) was sufficiently protective on the basis that:

1. The mechanisms for emesis in mink are likely to be similar to the mechanisms for emesis in humans (for example, activation of receptors in both the gastrointestinal tract and central nervous system).
2. The speed to onset (approximately 30 minutes) and the duration of T-2- and HT-2-induced emesis is proportional to the administered dose suggesting that it is likely to be dependent on the maximum (or peak) concentration in serum or plasma (C_max) rather than area under the concentration–time curve.
3. The point of departure is based on a gavage study where higher C_max are expected compared with equivalent dietary exposures.

DAS also induces emesis in mink via a similar mode of action, but at a relatively lower potency than T-2 and HT-2. Furthermore, similar to T-2 and HT-2, DAS has also induced reduced feed intake in mice via a similar mode of action.

Accordingly, the Committee established a group ARfD for T-2, HT-2 and DAS of 320 ng/kg bw (rounded down).

Considering the highly comparable nature of the methods used in studies concerning the emetic effects of T-2, HT-2 and DAS in mink, the Committee recommended a relative potency factor of 0.2 for acute exposure to DAS.

Group tolerable daily intake (TDI)

The Committee concluded that the most sensitive, reliable and reproducible effects observed following repeated dietary exposure were reported in the 3-week toxicity study in juvenile pigs. This study adequately characterized the test material and background exposure to common mycotoxins detected in feed and examined critical toxicological
effects at relatively low doses (for example, <25 µg/kg bw per day). The Committee also noted that juvenile pigs have been identified previously as a species sensitive to the emetic and haematotoxic effects of trichothecenes. Dose–response analysis of body weights, daily body weight gain and daily feed intake was conducted and a BMDL10 of 1.8 µg/kg bw per day based on reduced daily body weight gain was selected as the most appropriate point of departure for establishing a health-based guidance value.

Considering that the critical effect (i.e. nausea-induced reductions in feed intake resulting in decreased body weight gain) is likely to be Cmax-dependent and given the Committee’s low confidence in the overall toxicological database, a composite uncertainty factor of 72 was considered appropriate (eightfold as for the group ARID; threefold for extrapolation from subacute to chronic exposure and threefold for other uncertainties in the database). Accordingly, the Committee established a group TDI of 25 ng/kg bw for T-2, HT-2 and DAS, alone or in combination. The previous group provisional maximum tolerable daily intake (PMTDI) of 60 ng/kg bw for T-2 and HT-2, established at the fifty-sixth meeting and amended at the eighty-third meeting to include DAS, was withdrawn.

Although comparative longer-term data on T-2, HT-2 and DAS are not available, the Committee concluded that the relative potency factor of 0.2 is applicable for exposure durations longer than acute, due to the similar critical effects observed following acute and repeated oral exposures. The relative potency factor of 0.2 should be applied in comparing dietary exposure to DAS with the group TDI.

### Risk characterization

#### Acute dietary exposure

Acute dietary exposure to the sum of T-2 and HT-2 was previously evaluated at the ninetieth meeting of the Committee. The highest upper bound (UB) 95th percentile exposure estimate of 170 ng/kg bw was reported for infants in European countries. The Committee also noted that the acute dietary exposure estimates decreased with increasing age. The current Committee noted that acute exposure to DAS was not evaluated at its eighty-third meeting.

There is insufficient information available to estimate combined acute exposure to T-2, HT-2 and DAS. The dietary exposure estimates for T-2 and HT-2 calculated by the Committee at its ninetieth meeting are below the ARFD of 320 ng/kg bw. UB estimates of acute dietary exposure to the sum of T-2 and HT-2 (first tier) indicate no health concern, but estimates of dietary exposure to DAS in combination with T-2 and HT-2 should be carried out at a future meeting of the Committee when sufficient and suitable data on DAS become available.

#### Chronic dietary exposure

The estimates of dietary exposure to the sum of T-2 and HT-2 reviewed mainly related to European and north African countries. The estimates of chronic dietary exposure to the sum of T-2 and HT-2 derived from the literature for the general population for the lower bound (LB) mean ranged from 0.3 to 53 ng/kg bw per day and for the LB 95th percentile from 1.9 to 210 ng/kg bw per day. The Committee concluded that dietary exposure estimates for the sum of T-2 and HT-2 at the mean and at the 95th percentile are higher than the group TDI of 25 ng/kg bw, indicating a possible health concern. Estimates of chronic dietary exposure to DAS in combination with T-2 and HT-2 should be carried out at a future meeting of the Committee when sufficient and suitable data on DAS become available.

### Recommendations

The Committee recommended the following:

1. development of analytical multi-mycotoxin methods and standards for the quantification of type A trichothecenes and their various metabolites that occur in planta;
2. research on the spatial distribution of T-2 and HT-2 in agricultural commodities to ensure standard sampling methods for mycotoxins are appropriate;
3. that occurrence data for T-2, HT-2 and DAS from a wider range of countries be generated using analytical methods with suitably low LODs, to decrease the uncertainty in dietary exposure estimates and confirm the geographical distribution of these toxins;

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1 Historically, JECFA has used the term ‘provisional’, as there is often a paucity of reliable data on the consequences of human exposure at low levels, and new data may result in a change to the tolerable level. However, as any HBGV would be revisited if new data indicated the need for a change, and as the word maximum is redundant, it is recommended that the terms ‘provisional’ and ‘maximum’ no longer be used – that is, using only the terms tolerable daily intake (TDI), tolerable weekly intake (TWI) and tolerable monthly intake (TMI), as appropriate. Tolerable intake values are expressed as an amount (often in micrograms) per kilogram of body weight, as a single value and not a range, and normally using only one significant figure. World Health Organization/International Programme on Chemical Safety (2020). Principles and methods for the risk assessment of chemicals in food. Environmental Health Criteria 240, Chapter 5 (second edition). Geneva: World Health Organization (https://cdn.who.int/media/docs/default-source/food-safety/publications/chapter5-dose-response.pdf?sfvrsn=32edc2c6_5).
4. conducting chronic toxicity studies of T-2, HT-2 and DAS with adequate characterization of T-2, HT-2 and DAS doses as well as the background concentrations of other related mycotoxins in the basal feed; and
5. additional information on the toxicity of relevant (for example, those that co-occur) mycotoxin mixtures.
Annex 1

Ninety-third meeting of the Joint FAO/WHO Expert Committee on Food Additives
Virtual meeting, 24, 25, 29, 30 March and 1 April 2022

Members
Dr A. Agudo, Unit of Nutrition and Cancer, Catalan Institute of Oncology, Barcelona, Spain
Dr S. Barlow, Brighton, East Sussex, England
Dr D.J. Benford, Cheddington (Bucks), England (Chairperson)
Dr N. Fletcher, Food Standards Australia New Zealand, Canberra, ACT, Australia
Dr U. Mueller, Perth, Australia (Rapporteur)
Mr M. Feeley, Ottawa, Canada
Dr G.S. Shephard, Cape Town, South Africa
Dr J. Schlatter, Zurich, Switzerland

WHO temporary advisers
Mr A. Afghan, Health Products and Foods Branch, Health Canada/Government of Canada, Canada
Mr P.J. Cressey, Institute of Environmental Science and Research Limited (ESR), Christchurch, New Zealand
Dr L. Edler, Dudenhofen, Germany
Dr Y. Kiparissis, Health Products and Foods Branch, Health Canada/Government of Canada, Canada
Dr E. Kirrane, US Environmental Protection Agency’s Center for Public Health and Environmental Assessment, Research Triangle Park, NC, United States of America
Dr J.-C. LeBlanc, Laboratory for Food Safety, French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Maisons-Alfort Cedex, France
Dr M. Wheeler, NIH/NIEHS Biostatistics and Computational Biology Branch, Research Triangle Park, NC, United States of America

FAO experts
Professor S. Edwards, Harper Adams University, Shropshire, England
Professor P.W. Li, Oil Crops Research Institute, Chinese Academy of Agricultural Sciences, Wuhan, China

Secretariat
Dr V. Fattori, Food Systems and Food Safety Division, Food and Agriculture Organization of the United Nations, Rome, Italy (FAO Secretariat)
Ms N.Y. Ho, Department of Nutrition and Food Safety, World Health Organization, Geneva, Switzerland (WHO Joint Secretariat)
Dr M. Lipp, Food Systems and Food Safety Division, Food and Agriculture Organization of the United Nations, Rome, Italy (FAO Secretariat)
Mr K. Petersen, Department of Nutrition and Food Safety, World Health Organization, Geneva, Switzerland (WHO Joint Secretary)
Ms S. Kaplan, Bern, Switzerland (WHO Technical Editor)
Annex 2

Future work and recommendations

The Committee recommended the following:

1. Development of analytical multi-mycotoxin methods and standards for the quantification of type A trichothecenes and their various metabolites that occur in planta;
2. Research to investigate the spatial distribution of T-2 and HT-2 in agricultural commodities to ensure standard sampling methods for mycotoxins are appropriate;
3. That occurrence data for T-2, HT-2 and DAS from a wider range of countries be generated using analytical methods with suitably low LODs, to decrease the uncertainty in dietary exposure estimates and confirm the geographical distribution of these toxins;
4. Conducting chronic toxicity studies of T-2, HT-2 and DAS with adequate characterization of T-2, HT-2 and DAS doses as well as the background concentrations of other related mycotoxins in the basal feed; and
5. Additional information on the toxicity of relevant (for example, those that co-occur) mycotoxin mixtures.
Annex 3

Procedural matters
The ninety-third meeting of JECFA was held on 24, 25, 29, 30 March and 1 April 2022. Because of the travel restrictions and lockdowns due to the COVID-19 pandemic in many countries, it was not possible to convene an in-person meeting and the meeting was held online by video-conferencing. In view of the time differences in the countries of origin of the invited experts, the only possible time for a videoconference was restricted to a 3-hour time slot (12:00–15:00 CET) each day. This allowed only 30% of the usual daily length (8–10 hours) of a JECFA meeting.

Although the experts participated fully, they noted that an online meeting does not permit the necessary in-depth, robust scientific discussions and that online meetings are therefore not a suitable substitute for face-to-face meetings for JECFA. In particular, the experts felt that the online format did not foster the atmosphere of trust, inclusiveness and openness that has marked all JECFA meetings. The experts considered that the success of the ninetieth meeting was due to a large extent to the cohesion between them, which resulted from the trust generated during previous face-to-face meetings.

The experts decried the significant difficulty of meeting informally outside the scheduled meeting times because of the widely differing time zones. They noted that such informal interactions during physical meetings are instrumental to solving problems and to discussing issues in depth, bilaterally or in small groups, and added that such informal meetings often gave rise to solutions to stubborn problems. The inability to hold such meetings was considered to have impeded progress at the current meeting, as lack of sufficient time for discussion had slowed progress in developing safety evaluations.

The experts emphasized further that an invitation to a physical JECFA meeting at FAO or WHO headquarters gives rise to significantly more recognition by the expert’s employer of the weight, reach, responsibility and workload required for full participation in a JECFA meeting. The same degree of recognition was not granted by employers for this online meeting, as the experts remained available locally. This lack of recognition of the workload and significance of participation in a JECFA meeting led to an increase in other demands on experts, resulting in distraction and more frequent scheduling conflicts. The experts concluded that, cumulatively, such factors would be counterproductive for participation in future JECFA meetings if FAO and WHO maintained the online-only format.

In recognition of the difficulties and the tremendous effort made, the joint FAO/WHO Secretariat expresses its deep gratitude to all the experts for their commitment and flexibility, not least as the scheduled meeting times were exceedingly inconvenient for many.

The meeting report was adopted on 1 April 2022.