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1040

Evaluation of certain contaminants in food

Ninety-third report of the Joint FAO/WHO Expert Committee on Food Additives

Food and Agriculture Organization of the United Nations

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Virtual meeting, 24 March – 1 April 2022

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List of abbreviations and acronyms

ARfD	acute reference dose
BMD	benchmark dose
BMDL	lower 95% confidence limit on the benchmark dose
BMR	benchmark response
CCCF	Codex Committee on Contaminants in Foods
C_{max}	maximum (or peak) concentration in serum or plasma
CNS	central nervous system
DAS	4,15-diacetoxyscirpenol
DON	deoxynivalenol
EFSA	European Food Safety Authority
ELISA	enzyme-linked immunosorbent assay
GC	gas chromatography
GLP	good laboratory practice
HBGV	health-based guidance value
HPLC-MS	high-performance liquid chromatography–mass spectrometry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KBD	Kaschin–Beck disease
LB	lower bound
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantitation
MAS	monoacetoxyscirpenol
NEO	neosolaniol
NOAEL	no-observed-adverse-effect level
SCF	Scientific Committee on Food
SCR	scirpentriol
TDI	tolerable daily intake
UB	upper bound

1. Introduction

The ninety-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was convened by videoconference on 24, 25, 29 and 30 March and 1 April 2022. The meeting was opened on behalf of the Director-General of the World Health Organization (WHO) by Dr Moez Sanaa (Unit Head, Standards and Scientific Advice on Food and Nutrition, Department of Nutrition and Food Safety) and on behalf of the Director-General of the Food and Agriculture Organization (FAO) by Dr Markus Lipp (Food Systems and Food Safety Division, FAO). Dr Sanaa in his opening remarks welcomed all meeting participants, and stressed that, despite the challenges of the travel restrictions, the work of JECFA had progressed and continued to provide sound scientific advice to Codex and the Member States, largely thanks to the efforts and work of the JECFA experts.

Dr Markus Lipp welcomed all meeting participants on behalf of FAO and thanked all experts for their commitment and dedication to the work of JECFA. He underlined the importance of their work in relation to the work of the Codex Alimentarius Commission in developing international food safety standards.

1.1 Procedural matters

Owing to the travel restrictions and lockdowns due to the COVID-19 pandemic in many countries, it was not possible to convene a physical meeting and it was instead decided to hold it online by videoconferencing. 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. The time allocated for the meeting was shorter than usual as only the toxicological assessment and risk characterization of trichothecenes T-2 and HT-2 toxins (addendum) was scheduled for discussion.

All participating experts reaffirmed that online meetings did not permit the necessary in-depth, robust scientific discussions that have been a characteristic of past JECFA physical meetings and therefore were not a suitable substitute. In particular, the experts felt that the online format did not foster the atmosphere of trust, inclusiveness and openness that has marked all JECFA physical meetings. The experts considered that the success of the ninety-third meeting was mainly due to the cohesion between them, which stemmed from the trust built on the relationships they had formed during previous face-to-face meetings. The experts also decried the significant difficulty of holding any informal meetings outside the scheduled meeting times because of the widely differing time zones. They noted that such informal interactions during the physical meetings were instrumental in solving problems and discussing issues in depth, bilaterally or in

small groups, and added that such informal settings often gave rise to equitable solutions to difficult problems.

The experts emphasized that an invitation to a physical JECFA meeting at the FAO or WHO headquarters gives rise to a more significant 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 acknowledgement 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 the experts, resulting in greater distractions 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 efforts made, the Joint FAO/WHO Secretariat expressed 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.

1.2 Declarations of interests

The Secretariat informed the Committee that all experts participating in the ninety-third JECFA meeting had completed a declaration of interest form. The declarations were assessed as to the extent to which any interest could be reasonably expected to influence the experts' judgement. The declared interests were considered unlikely to impair the individual's objectivity or have any significant influence on the impartiality, neutrality and integrity of the work. Neither FAO nor WHO received any public comments in response to the online posting of the names and brief biographies of the individuals considered for participation in the expert meeting. The interests of all participants were disclosed at the beginning of the meeting to all meeting attendees.

1.3 Adoption of the agenda

The meeting agenda was adopted without any modification.

2. Trichothecenes T-2 and HT-2 toxins (addendum)

2.1 Explanation

T-2 toxin (T-2) and HT-2 toxin (HT-2) are type A trichothecene mycotoxins, which are structurally-related epoxy sesquiterpenoids. Surveys have revealed the presence of T-2 and HT-2 in a wide range of foodstuffs but they are primarily contaminants of cereals and cereal-based products. T-2 and HT-2 have been reported to be produced by *Fusarium acuminatum*, *F. equiseti, F. langsethiae, F. poae*, *F. sibiricum* and *F. sporotrichioides*.

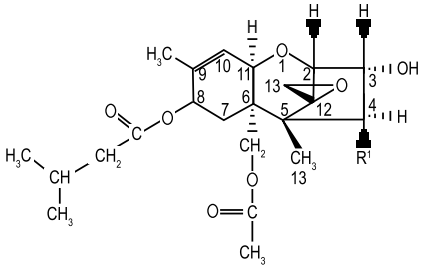
T-2 is the trivial name for 4β,15-diacetoxy-3α,dihydroxy-8α-[3-methylbutyryl-oxy]-12,13-epoxytrichothec-9-ene (CAS number 26934-87-2). HT-2 is the trivial name for 15-acetoxy-3α,4β-dihydroxy-8α-[3-methyl-butyryloxy]-12,13-epoxytrichothec-9-ene (CAS number 21259-20-1). The structures of T-2 and its metabolite HT-2 differ only in the functional group at the C4 position (Fig. 1). HT-2 is formed from the deacetylation of T-2, which can occur as a result of metabolism in the fungus, the infected plant or in animals after ingestion. These toxins co-occur with several other type A trichothecenes (for example, 4,15-diacetoxyscirpenol (DAS) and neosolaniol (NEO)) and modified mycotoxins – phase I and II metabolites formed in the fungus or the infected plant (for example, T-2 triol and T-2-3-glucoside).

T-2 and HT-2 were previously evaluated by the Committee at its fifty-sixth meeting (Annex 1, reference *152*). The Committee concluded at that meeting that there was substantial evidence for the immunotoxicity and haematotoxicity of T-2 in several species, and that these are critical effects after short-term intake. The Committee further concluded that the safety of food contaminated with T-2 could be evaluated from the lowest-observed-adverse-effect level (LOAEL)[1] of 29 µg/kg bw per day for changes in white and red blood cell counts identified in the 3-week dietary study in pigs. The Committee used this LOAEL and a safety factor of 500 to derive a provisional maximum tolerable daily intake (PMTDI)[2] for T-2 of 60 ng/kg bw. The Committee further concluded that the toxic effects

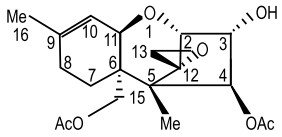
[1] Prior to the sixty-eighth meeting of the Committee (Annex 1, reference *187*), a NOAEL would have been termed a no-observed-effect level (NOEL) and a LOAEL would have been termed a lowest-observed-effect level (LOEL).

[2] "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 [health-based guidance value] 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" *(3)*.

Fig. 1
Chemical structures of T-2, HT-2 and DAS



T-2 (R_1 = OAc) and HT-2 (R_1 = OH) toxins



4,15-DAS

of T-2 and its metabolite HT-2 could not be differentiated, and hence HT-2 was included in the PMTDI, resulting in a group PMTDI of 60 ng/kg bw for T-2 and HT-2. At its eighty-third meeting in 2016, the Committee included DAS in the group PMTDI of 60 ng/kg bw for T-2 and HT-2 (Annex 1, reference *233*).

In response to a request from the Codex Committee on Contaminants in Foods (CCCF) for an updated evaluation, including an exposure assessment on T-2 and HT-2, these compounds were evaluated by the present Committee. At the ninetieth JECFA meeting (Annex 1, reference *247*), information published since 2001 on T-2 and HT-2 concerning analytical methods, sampling, effect of processing, prevention and control, occurrence in food commodities and dietary exposure was reviewed. For ease of reading and for the sake of completeness, text from the report of the ninetieth meeting is included below (indented and printed in smaller type).

For this evaluation, previous assessments (monographs) completed by JECFA, the Scientific Committee on Food (SCF), or the European Food Safety Authority (EFSA), and national and regional governmental authorities were identified. This was followed by a comprehensive literature search to identify any critical new data for the assessment of human health risk. The cut-off dates for inclusion in this report were 1 January 2000 to 24 December 2021.

Numerous publications on the toxicity of T-2 and HT-2 in poultry have become available since the Committee's previous evaluation in 2001 (Annex 1, reference *152*). Considering the acknowledged physiological differences between

poultry and humans *(1, 2)* and the overall availability of information on other more relevant experimental models (for example, mice, rats, rabbits and pigs), the following summaries of biochemical and toxicological aspects of T-2 and HT-2 do not include information from experiments in poultry.

2.2 Biochemical aspects

Recent studies have confirmed that T-2 and its conjugates are readily transformed by microbial activity into at least 20 metabolites in the gastrointestinal tract of mammals, with HT-2 being the predominant metabolite (Annex 1, reference *152, 153*; *4–8*). Following oral dosing with 1 mg/kg bw of HT-2, none could be detected in the plasma of rats. However, a C_{max} for the downstream hydroxylated metabolite, 3′-OH HT-2 was observed only 10 minutes after oral administration of HT-2 (*9*). The T-2 metabolites identified using isolated liver cells from several mammalian species in vitro confirmed the potential of phase I and phase II metabolism (Annex 1 reference *152*; *9–12*). These biotransformations, in combination with the microbial activity in the gastrointestinal tract, ensure that T-2 undergoes substantial presystemic metabolism.

Four hours after intravenous administration of T-2 to pigs, the largest combined concentration of unchanged T-2 and its metabolites (including glucuronide conjugates) was detected in the gastrointestinal tract (Annex 1 reference *152*). The highest unchanged T-2 concentration was detected in fat tissues of pigs, followed in order by lungs and spleen (*13, 14*). Probably owing to its lipophilicity, unchanged T-2 has been detected in the milk of nursing mammals (Annex 1 reference *152*; *15*).

2.3 Toxicological studies

The Committee (Annex 1, reference *152*) reported that strain and sex differences in susceptibility to the toxicity of T-2 have been observed in mice following acute gavage and inhalation dosing, with female mice exhibiting greater evidence of toxicity at lower doses than male mice. Following acute oral or intraperitoneal exposure, T-2 induces oxidative stress, decreased feed intake, emetic, immunotoxic, haematotoxic, hepatic, renal and neurotoxic effects in a variety of experimental animals. Based on the available evidence, emesis and decreased feed intake in mink and mice, respectively, appear to be sensitive toxicological end-points following acute exposure to both T-2 and HT-2. For example, Wu et al. *(16)* identified a NOAEL of 5 μg/kg bw T-2 or HT-2 (via gavage) in female mink based on an increased incidence of emesis at doses ≥ 50 μg/kg bw T-2 or HT-2 following single-dose gavage or intraperitoneal exposure. Similarly, Wu et

al. *(17)* identified a NOAEL of 10 µg/kg bw T-2 or HT-2 in female mice based on statistically significant decreases in feed intake at doses ≥100 µg/kg bw T-2 or HT-2, 0–3 hours following single-dose gavage exposure or 0–6 hours following intraperitoneal exposure. Both emesis in mink and decreased feed intake in mice were associated with elevated plasma concentrations of hormones typically associated with central nervous system (CNS)-related mechanisms for satiety that also operate in humans (*16, 18–20*).

In the Committee's previous evaluation of T-2 and HT-2 (Annex 1, reference *152*), the immune system (for example, changes in leukocyte counts, delayed hypersensitivity, depletion of selective blood cell progenitors, depressed antibody formation, allograft rejection and a blastogenic response to lectins, and decreased and increased resistance to microbial infection) was identified as the target for T-2 toxicity following short-term exposure. However, it was also noted that feed refusal, reduced weight gain and changes in organ weights are also sensitive toxicological end-points that have been observed in various animal species exposed to T-2 and that the potential effects of reduced feed intake and decreases in body weight gain on the observed immunological end-points could not be evaluated.

The effect of feed refusal and reduced weight gain on immunological end-points was supported by a 6-week dietary study in mice by Friend et al. *(21)* who used pair-fed control animals. Specifically, Friend et al. *(21)* showed that spleen weight, cell counts and lymphoproliferative response were similarly reduced in animals from the pair-fed control group as compared to the animals exposed to T-2 (20 mg/kg diet) for up to 6 weeks. Friend et al. *(21)* suggested that the response of the pair-fed control animals was due to protein deficiency, which reduced non-splenic phagocytic cells. This suggestion is supported by WHO/IPCS *(22)*, which indicates that protein calorie restriction and deficiencies of trace elements such as zinc have been associated with immunosuppression and that nutritional status and stressful conditions influence the pathology of lymphoid organs such as the thymus. Since short-term caloric restriction has been shown to reduce both thymic and splenic weight and correspondingly, to affect the numbers of thymocytes and lymphocytes *(23–25)*, the T-2-induced immunotoxicity/haematotoxicity may be partially related to the reduced feed intake caused by T-2 exposure. The Committee (Annex 1, reference *152*) also indicated that the immune response to T-2 exposure varied depending at least in part on the dose and how long after administration the effects were measured. For example, both increased and decreased leukocyte counts and increased and decreased resistance to microbial infection have been reported.

Table 1 summarizes the results of studies that were considered relevant to the hazard characterization update of T-2 and HT-2. For ease of comparison, dietary concentrations were converted to doses in Table 1. However, most of the

Table 1
Summary of key toxicity studies of T-2 and HT-2

Species/study type (route of administration)	Doses	Critical effect(s)	NOAEL	LOAEL
Acute oral toxicity in mink (gavage)				
Wu et al. (2016) *(16)*	0, 5, 50, 250 or 500 µg/kg bw T-2 or HT-2	Significantly increased incidence of emesis was observed at doses ≥ 50 µg/kg bw T-2 or HT-2 following single-dose gavage or intraperitoneal exposure	5 µg/kg bw	50 µg/kg bw
Acute oral toxicity in mice (gavage)				
Wu et al. (2015) *(17)*	0, 10, 100, 500 or 1000 µg/kg bw T-2 or HT-2	Statistically significant decreases in feed intake were observed at doses ≥100 µg/kg bw T-2 or HT-2 following single-dose gavage or intraperitoneal exposure	10 µg/kg bw	100 µg/kg bw
Short-term oral toxicity in rabbits (gavage)				
Kovács et al. (2013) *(26)* 65 days	0, 10, 20 or 50 µg/kg bw per day via gavage	Decreased feed intake, histopathology in the testes and liver and a slower increase in gonadotropin-releasing hormone (GnRH)-induced testosterone synthesis were observed at doses ≥ 20 µg/kg bw per day	10 µg/kg bw per day	20 µg/kg bw per day
	0, 10 or 20 µg/kg bw per day via the diet	Kovács et al. (2013) showed that these effects were not observed following dietary exposure to T-2 at equivalent doses up to 20 µg/kg bw per day (highest dose tested) for 65 days	20 µg/kg bw per day	–
Short-term oral toxicity in juvenile pigs (diet)				
Rafai et al. (1995) *(27, 28)* 21 days	0, 500, 1000, 2000 or 3000 µg/kg diet	No NOAEL could be identified, as effects were observed at all doses	–	~25 µg/kg bw per day[e]
	Equal[a] to 25, 52, 103 or 125 µg/kg bw per day T-2	Significantly reduced feed intake, reduced daily weight gain, reduced leukocyte count, decreased proliferative response of lymphocytes to concanavalin A, and reduced horse globulin antibody titre were observed at ≥ 25 µg/kg bw per day		
		See Annex 1, reference *153*: and Section 2.2.2(d) for detailed summaries		
Meissonnier et al. (2008, 2009) *(29, 30)* 28 days	0, 540, 1324, 2102 µg/kg diet	Decreased anti-OVA titres were observed at doses greater than or equal to approximately 68 µg/kg bw per day. No cellular depletion of the Peyer's patches in the ileum or in the spleen was observed compared to controls. Lymphocyte proliferation in response to concanavalin A and ovalbumin was similar in controls and in all treated animals.	~27 µg/kg bw per day	~68 µg/kg bw per day
	Equivalent[b] to 0, 27, 68 or 108 µg/kg bw per day T-2	Feed intake values were not reported; consequently, dose estimates may not reflect actual dosing		
Rafai et al. (2013) *(31)* 21 days	0, 300 (11.2) or 500 (18.0) µg/kg diet	No NOAEL could be identified since effects were observed at all doses, i.e. at 11.2 and 18.0 µg/kg bw per day, significantly decreased feed intake (22 and 28% less than control, respectively), terminal body weights (10 and 16% less than control, respectively) and daily body weight gain (24 and 36% less than control, respectively) were observed. The authors stated that no difference from the controls was observed for lymphocyte proliferation (as induced by	~27 µg/kg bw per day	~68 µg/kg bw per day

Table 1 (continued)

Species/study type (route of administration)	Doses	Critical effect(s)	NOAEL	LOAEL
	Equal[a] to 0, 11.2 or 18 µg/kg bw per day T-2	purified horse globulin, phytohaemagglutinin and concanavalin A) and anti-horse globulin antibody titre	–	11.2 µg/kg bw per day
Verbrugghe et al. (2012) *(32)* 18 days	0, 15 or 83 µg/kg diet	The average daily body weight gain of the high-dose group was significantly lower than in the controls (27% of control)	0.6 µg/kg bw per day	3.1 µg/kg bw per day
	Equivalent[c] to 0.6 or 3.1 µg/kg bw per day T-2	Feed intake was not measured; consequently, dose estimates may not reflect actual dosing		
Subchronic oral toxicity in rats (diet)				
Rahman et al. (2014, 2016, 2021) *(33–35)*	0, 500, 750 or 1000 µg/kg diet	No NOAEL could be identified, as effects were observed at all doses	–	50 µg/kg bw per day
	Equivalent[d] to 0, 50, 75 or 100 µg/kg bw per day T-2	Significantly reduced survival, reduced body weight, reduced feed intake, changes in haematological and clinical chemistry parameters, and histopathology in the kidneys, spleen and thymus were observed at all concentrations. Statistically significant decreases in functional immune responses (anti-SRBC antibody titre, delayed-type hypersensitivity, concanavalin A lymphocyte stimulation) were also reported at all concentrations.		
		Feed intake values were not reported; consequently, dose estimates may not reflect actual dosing		
		Supporting information: Fadhil et al. (2021) *(36)* also observed evidence of oxidative stress and/or significant histopathology in the livers and small intestines of rats exposed to dietary concentrations of 470 µg/kg diet T-2 for 90 days. Similarly, histopathological lesions in the spleen, thymus, liver, kidneys, testes, heart and brain of rats exposed to concentrations as low as 250 µg/kg diet for 90 days were reported by Raut et al. (2013) *(37)*		

Anti-OVA, anti-ovalbumin; anti-SRBC, anti-sheep red blood cells; LOAEL, lowest-observed-adverse-effect level; NOAEL, no-observed-adverse-effect level.
[a] See Appendix for dose conversion calculations.
[b] Conversion factors of 0.0506 to 0.0516 mg/kg bw per day per mg/kg diet were calculated from Rafai et al. *(27)*, see Appendix.
[c] A conversion factor of 0.037 mg/kg bw per day per mg/kg diet was calculated from Rafai et al. *(31)*, see Appendix.
[d] A conversion factor of 0.01 mg/kg bw per day per mg/kg diet was used.
[e] JECFA (Annex 1, reference *152*) and Rafai et al. *(27, 28)* report doses of 29, 62, 100 and 130 µg/kg bw per day, which are different from those calculated by the current Committee as described in Appendix.

dietary studies summarized did not record feed intake. Since feed intake is a sensitive toxicological end-point for T-2, the Committee noted that the estimated doses using default conversion factors may overestimate actual exposures.

The Committee noted that the toxicological database was limited for the purpose of establishing a health-based guidance value (HBGV). For example, many of the studies investigated adverse effects at high doses. The actual intake of the test material and the presence of other related mycotoxins in the basal feed

was inadequately described, and none of the identified studies that reported the effects of low doses (for example, ≤ 25 µg/kg bw per day) followed standard testing guidelines according to good laboratory practice (GLP) standards. Furthermore, the Committee noted some discordance concerning some of the effects at low doses. Nevertheless, the lowest LOAEL reported is approximately 3 µg/kg bw per day T-2. This comes from a study by Verbrugghe et al. *(32)* who noted a significant decrease in daily body weight gain with a NOAEL of approximately 0.6 µg/kg bw per day T-2 in juvenile pigs exposed to diets containing 0, 15 or 83 µg/kg diet T-2 for 18 days. Obremski et al. *(38)*,[1] Wojtacha et al. *(39)*, Makowska et al. *(40, 41)* and Rychlik et al. *(42)* observed haematological and neurochemical changes in the gastrointestinal tract of pigs exposed to low oral doses of T-2 (for example, ~7 to 14.5 µg/kg bw per day) for 42 days.

As expected, gavage exposure induces effects at lower doses than dietary exposure *(26)*. Additionally, effects mediated through the gastrointestinal system (for example, decreased feed intake and/or body weight gain) appear to be observed at or below doses that induce functional effects on the immune system and other systemic effects. For example, Rafai et al. *(31)* and Meissonnier et al. (*29)* showed that functional effects on the immune system (i.e. decreased antibody responses to horse globulin or ovalbumin) of juvenile pigs were not observed at doses close to or below the previously identified LOAEL of 29 µg/kg bw per day (Annex 1, reference *152*). The Committee also noted that there was inconsistency in the antibody response to horse globulin or ovalbumin in these studies *(28, 29, 31)*. Although it is difficult to conclusively identify the cause of the inconsistency, the Committee noted that the authors had used a novel protocol. Validated methods to assess T-cell-dependent antibody responses typically use well-characterized antigens such as sheep red blood cells or keyhole limpet haemocyanin, rather than a protein mixture such as horse globulin with its corresponding highly variable antigenicity profile *(43)*. Additionally, there was no information in either the study by Rafai et al. *(31)* or the one by Meissonnier et al. *(29)* regarding the time interval for a peak antibody (IgM and IgG) response or the use of a positive control (for example, cyclosporin or cyclophosphamide) to validate the performance of the immune function assay.

Significant effects on feed intake were observed at doses as low as 11.2 µg/kg bw per day *(31)*. Evidence of reduced feed intake and/or growth at doses slightly less than those required for functional changes in the immune system is consistent with what is observed with related trichothecenes such as DAS (Annex 1 reference *235*) and DON (Annex 1, reference *152*). Considering this and the previously mentioned association of reduced feed intake with changes in immunological

[1] The dose estimate in Obremski et al. *(38)* used the conversion factors for pigs calculated from Rafai et al. *(31)* (see Appendix) and a dietary concentration of 0.2 mg/kg diet T-2.

and haematological parameters (Annex 1, reference *152*; *21–25*), the Committee identified reduced body weight, daily body weight gain and daily feed intake observed in juvenile pigs as critical effects for short-term oral T-2 exposure. Subchronic dietary studies of T-2 in rats *(33–35)* were also considered. However, the Committee identified various limitations associated with these studies, which made their application to the overall hazard characterization difficult:

- The lowest estimated dose was more than fourfold higher than the lowest dose in the Rafai et al. study in juvenile pigs *(31)*.
- Severe effects were observed in the lowest dose group, thereby limiting the relevance of the observed effects on haematological and immunological parameters.
- Feed intake was not recorded, thereby limiting accurate dose estimates.
- Other mycotoxins could have been present in the test material.

No additional long-term studies of toxicity and carcinogenicity were identified. Previously, the Committee had summarized the results of a long-term (71-week) dietary study in male and female mice (Annex 1, reference *152*). It noted a statistically significant increase in the incidence of pulmonary and hepatic adenomas in male mice at relatively high dietary concentrations (3 mg/kg diet; equivalent to 450 µg/kg bw per day), with no significant increase in tumour incidence in females. Although positive results have been observed in several in vitro and in vivo genotoxicity tests, the Committee noted that inhibition of DNA and RNA synthesis by T-2 has been reported at concentrations generally exceeding those that cause inhibition of protein synthesis. In line with the Committee's previous conclusions (Annex 1, reference *152*), the current Committee concluded that the mode of action of T-2-induced toxicity is unlikely to include direct interaction with DNA.

Based on the available evidence, reproductive and developmental effects are not expected to occur below doses that have been identified as eliciting reduced feed intake and decreased body weight gain, as well as immunotoxicity or haematotoxicity. For example, the Committee (Annex 1, reference *152*) previously reported that reproductive or gross developmental effects were not observed at doses as low as 220 µg/kg bw per day in a two-generation study in mice *(44)*.

2.4 Related trichothecenes

Although not the focus of this evaluation, the comparative effects of T-2 and HT-2 and other mycotoxins were briefly reviewed. In a previous evaluation of DAS, the

Committee concluded that T-2 and HT-2 are structurally similar to DAS (Annex 1, reference *235*). There was also evidence that they cause similar effects at the biochemical and cellular levels, have similarities in their toxic effects in vivo and have an additive dose effect when co-exposure occurs. According to the previous Committee (Annex 1, reference *235*), although T-2 appears to be more potent than DAS in vitro and in vivo, the available data were insufficient for establishing relative potencies. Of the few studies that considered the combined effects of DAS and T-2, a consistent additive dose effect was observed for end-points such as in vitro inhibition of protein synthesis and lymphocyte proliferation, oral lethal doses following acute exposure, and the incidence of oral lesions, feed refusal and decreased egg production following short-term dietary exposure in chickens.

Based on more recent information, the current Committee noted that acute oral exposure to DAS has effects on feed intake in mice *(45,46)* and emetic response in mink *(47)*, via a similar mode of action to T-2 and HT-2. Other structurally similar trichothecenes (for example, neosolaniol (NEO), deoxynivalenol (DON), 3-acetyldeoxynivalenol (3-ADON), 15-actetyldeoxynivalenol (15-ADON), fusarenon-X (FUS-X) and nivalenol (NIV)) have also shown similar toxicological effects and biochemical changes to T-2 and HT-2. However, additivity, synergism and antagonism have been observed depending on the mycotoxin mixture, the cell culture or animal species investigated, dose or concentration, duration of exposure and/or the effects measured. The Committee noted that there is limited information concerning co-occurrence of mycotoxins (Annex 1, reference *247*; *48, 49*) and that the available literature concerning mycotoxin mixture toxicology is very limited.

As previously recommended (Annex 1, reference *235*), the Committee considered the possibility for additivity with respect to DAS and T-2 and HT-2 exposure. In particular, the present Committee noted that this conclusion 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 with a lower relative potency *(47)*. Less comparative information was available with respect to other toxicologically relevant end-points (for example, immunotoxicity and haematotoxicity, hepatotoxicity and renal toxicity) following acute or repeated oral exposure. The current Committee reconfirmed the inclusion of DAS in the group tolerable daily intake (TDI) for T-2 and HT-2, as proposed at the eighty-third JECFA meeting. The current Committee concluded that new data were sufficient to recommend a relative potency factor for DAS (see Table 5 in section 2.14.1). Although comparative longer-term data on DAS and T-2 and HT-2 are not available, the Committee concluded that the relative potency factor would be likely to be applicable for exposure scenarios longer than acute, due to the similar critical effects observed following acute and repeated oral exposures.

2.5 Observations in domestic animals/veterinary toxicology

Although a case report of T-2-related poisoning in sheep was identified *(50)*, the possibility of other mycotoxins contributing to the observed effects could not be adequately ruled out. The previous Committee noted that cats were more susceptible to the toxicity of T-2 than other species, most likely due to their demonstrated deficiency in glucuronide conjugation (Annex 1, reference *152*).

2.6 Observations in humans

Several studies monitoring the presence of type A trichothecenes in urine were identified. All of them used a multi-biomarker approach measuring multiple mycotoxins and their metabolites: a few studies measured levels in the blood as well, but these were below the limit of detection (LOD). Overall, the data available point to a very low level of T-2, HT-2 and DAS in urine. One study compared mycotoxin levels in urine with 24-hour dietary recall data to determine the extent of concordance *(51)*. Of the adults for whom urine samples were available, T-2, HT-2 and DAS were detected in 22%, 6.4% and 13%, respectively. As only limited concordance was observed between the exposure estimates and mycotoxin (T-2, HT-2 and DAS) levels in urine, it was suggested that these analytes were insufficient to confidently determine the extent of dietary exposure. No studies of biomarkers of effect were identified.

DAS was investigated in the 1970s and 1980s as a potential chemotherapeutic agent for use in cancer patients (Annex 1, reference *235*). Several phase I and phase II clinical trials were conducted using an intravenous infusion, but they were discontinued due to the lack of efficacy, together with observations of adverse effects. The main adverse effects after acute and repeated exposure included myelosuppression, characterized by decreased levels of lymphocytes and platelets, emesis and hypotension. Mild nausea was reported at estimated doses of 41–65 µg/kg bw; more severe effects (vomiting, hypotension and myelosuppression) were reported at doses of approximately 81 µg/kg bw or above, with a dose-dependent increase in frequency and severity. No clinical or epidemiological studies of the effects of oral administration of DAS in humans have been identified. The Committee concluded that information available from human clinical studies was insufficient or not relevant for hazard characterization of dietary exposure to DAS.

Episodes of acute poisoning associated with ingestion of foods contaminated with *Fusarium* toxins were reported in 1931–1947 in the former Soviet Union. The pathological pattern included necrotic lesions of the oral cavity, oesophagus, and stomach and, in particular, pronounced leukopenia consisting primarily of bone-marrow hypoplasia and aplasia, and death. Poisoning events

associated with infected grains were also reported in Japan, "Korea" (1946–1963), China and India (1980s–1990s). These events were associated with nausea, vomiting, pharyngeal irritation, abdominal pain, diarrhoea, bloody stools, dizziness and chills. Subsequent analyses of suspected food or grain samples indirectly linked the reported outbreaks to T-2, but the concomitant occurrence with DON, acetyldeoxy-nivalenol, NIV or other trichothecenes cannot be completely ruled out (Annex 1, reference *152*). No new data on acute poisoning or outbreaks of toxicosis related to T-2 or HT-2 were identified.

Over the past two decades, several epidemiological studies have been published assessing the possible association of Kaschin–Beck disease (KBD) with exposure to trichothecenes. KBD is a form of chronic degenerative osteoarthropathy endemic to several Chinese provinces, the Democratic People's Republic of Korea and south-east Siberia. Results from ecological studies *(52)* and community intervention studies *(53)* suggest that prevalence and development of KBD is associated with the amount of T-2 in food. Moreover in vitro and in vivo experimental studies have shown chondrocyte toxicity of T-2 *(52)*. However, the etiology of the disease remains debatable; other risk factors proposed include selenium and iodine deficiency *(53)* and exposure to organic matter (fulvic and humic acid) in contaminated drinking water *(54)*. Given the likely multifactorial nature of KBD, the Committee concluded that a causal relationship between T-2 exposure and KBD could not be established with reasonable confidence. Therefore, the data on KBD had limited relevance for the present evaluation.

2.7 Analytical methods

The Committee reviewed the analytical methods for the determination of T-2 and HT-2 developed since the fifty-sixth meeting and noted considerable advances in methodology, particularly the development of multimycotoxin analytical methods based on high-performance liquid chromatography–mass spectrometry (HPLC-MS).

Although thin-layer chromatography has largely been superseded by more modern methods, reports of its use for T-2 and other trichothecenes can still be found. Screening methods, such as enzyme-linked immunosorbent assay (ELISA), lateral flow immunoassays, fluorescence polarization and various biosensors and chemosensors continue to be developed and commercialized based mainly on monoclonal antibodies. These assays can be tailored for detection of T-2 alone or the sum of T-2 and HT-2 combined.

Whereas the Committee noted at its fifty-sixth meeting that gas chromatography (GC) with derivatization and detection by electron capture or MS was the primary technique for quantification, there has been a strong shift away from GC towards the extensive use of HPLC. Depending on the extract clean-up technique, these toxins, either

alone or together with other type A and B trichothecenes, can be determined by HPLC with ultraviolet (UV) or fluorescence detection. For this purpose, several derivatizing agents have been described.

The major advance in routine analysis has been the development of HPLC-MS methods, which enable simultaneous quantification and confirmation. Although capable of targeted single analyte determination, these methods can be used for multimycotoxin determination in which T-2 and HT-2 can be determined as part of a suite of toxins and/or secondary metabolites. Modern methods achieve LODs in the low or sub-µg/kg range but require consideration of optimum conditions of extraction and extract purification to accommodate the differing chemistries of the target analytes. Two approaches for treating the extract are the "dilute-and-shoot" method in which the extract is injected into the HPLC after solvent dilution or the use of a generic clean-up (QuEChERS – quick, easy, cheap, effective, rugged and safe) to remove impurities such as lipids. A feature of MS detection, particularly with multimycotoxin determination using limited extract purification, is the occurrence of matrix effects. To overcome these problems, stable isotope-labelled internal standards or matrix-matched standards are used. Quantification can also be performed by the standard addition method. A T-2 and HT-2 certified reference material composed of ground oat flakes is available to aid method development and quality assurance. Modified forms of T-2 and HT-2, including numerous plant metabolites, can be identified by HPLC-MS/MS; however, validation and quantification is limited by the availability of analytical standards (Annex 1, reference *247*).

2.8 Sampling protocols

Currently, sampling methods for the analysis of T-2 and HT-2 in cereal grains use protocols developed for other mycotoxins. Many countries have their own sampling guidelines. For example, China uses GB/T 30642-2014, countries in Europe use EC 401/2006, and Canada and the United States of America (USA) have designated sampling guidelines *(55, 56)*. Additionally, sampling guidance is available from the Codex Alimentarius Commission (CAC/GL 50-2004). In recent years, the drive towards safer food has highlighted the need to determine levels of T-2 and HT-2 contamination in different food commodities. Therefore, it is important to simplify, harmonize and validate sampling plans for T-2 and HT-2 (Annex 1, reference *247*).

2.9 Effects of processing

In general, T-2 and HT-2 levels can be reduced by various processes commonly used in the food and feed industry. Cleaning and sorting are useful first steps in the reduction of T-2 and HT-2 contamination. T-2 and HT-2 are mostly located in the outer layers of

cereal grains, and are recovered in higher concentrations in husk, bran and germ relative to other milling fractions. Therefore, the by-products from sorting and milling should be strictly managed. T-2 and HT-2 concentrations decrease during cooking at about 150 °C. Higher temperatures increase the extent of degradation of the toxins. Fermentation can reduce levels of contamination by T-2 and HT-2, although pH, moisture, temperature and the fermentation organisms impact concentrations (Annex 1, reference *247*).

2.10 Prevention and control

Information on the prevention and control of T-2 and HT-2 is limited to a small number of studies in a few commodities (primarily oats) and these often agree with the greater volume of information available for the related trichothecene, deoxynivalenol (DON). For preharvest mitigation, decreased concentrations of T-2 and HT-2 are associated with having fewer cereals in rotation and growing resistant cultivars. Ploughing may also be beneficial, depending on the rotational position of the host crops. Unlike with DON, growing maize as a previous crop is not a risk factor and limited studies indicate fungicides do not reduce T-2 and HT-2 contamination. For postharvest mitigation, prevention of further T-2 and HT-2 production by *Fusarium* species is achieved by storing commodities at low moisture content. Various microbes, enzymes and chemicals have demonstrated ability to metabolize or degrade T-2 and/or HT-2, but these have been mainly tested in liquids and may not be technically feasible for most foodstuffs (Annex 1, reference *247*).

2.11 Levels and patterns of contamination in food commodities

When T-2 and HT-2 were assessed previously at the fifty-sixth meeting of the Committee, the percentages of analyses from 1990–2000 (n = 999) that exceeded 100 µg/kg were 0.4% and 0.9% for T-2 and HT-2, respectively. The value of 100 µg/kg was used by the Committee at that meeting to allow comparison to a previous study due to the wide range of LODs, which decreased over time *(57)*. In the current assessment of data from the GEMS/Food contaminants database, there were 49 912 samples analysed for T-2 and HT-2 from 2001 to 2020. Within this dataset 0.8% and 1.5% of samples exceeded 100 µg/kg T-2 and HT-2, respectively. It cannot be determined if these increases in reported frequency of high concentrations of T-2 and HT-2 are due to increases in the mycotoxin concentrations over time or to a greater focus on sampling in regions and/or commodities with higher levels of T-2 and HT-2.

Based on data from the GEMS/Food contaminants database, comparison of analyses for T-2 and HT-2 across global regions has identified stark differences in the number of tests reported, the distribution of foodstuffs analysed and the analytical results. Most of the analytical records were submitted by the European Region, with limited

numbers submitted by a few countries within the other regions. Some of these countries only submitted results for a single foodstuff (sorghum from four African countries and cassava from the USA). Three countries in the Western Pacific Region submitted analytical results for a wide variety of foodstuffs, but they were mostly negative. Canada also submitted results for a wide variety of foodstuffs, with 1.5% positive samples, a lower bound (LB) mean concentration of 0.6 µg/kg, and a few samples with greater than 100 µg/kg combined T-2 and HT-2. In contrast, T-2 and HT-2 levels reported in Europe were much higher in cereals and any food category that does or may contain cereals. More detailed analysis of the European dataset showed that the highest levels were detected in oat, maize, barley and wheat grain (LB mean concentrations of 241, 24, 17 and 5.2 µg/kg, respectively) with significantly lower concentrations occurring in milled products, excluding bran and by-products.

Although limited in quantity, the literature generally supported the conclusion that T-2 and HT-2 levels are low in all regions of the world outside Europe. For example, a total diet study in sub-Saharan Africa analysed composite food samples (n = 194) representing food intake at eight locations across four countries (Benin, Cameroon, Mali and Nigeria) for numerous mycotoxins *(58)*. No samples had detectable T-2 or HT-2 (LOD = 0.4 and 0.8 µg/kg, respectively).

As with other *Fusarium* mycotoxins that are produced within the growing crop, their concentrations will fluctuate between growing seasons and regions, depending on climatic conditions. Most studies reporting T-2 and HT-2 concentrations are based on single-year surveys and the effect of seasonal variability cannot be assessed. A 7-year (2002–2008) investigation of *Fusarium* mycotoxins in harvested oats in the United Kingdom showed the annual combined mean concentration of T-2 and HT-2 ranged from 121 to 727 µg/kg *(59)*.

Recent studies have identified numerous modified mycotoxins that are the result of metabolism *in planta*; some have also been found to exist in naturally contaminated material. T-2 tetraol and HT-2-3-glucoside can occur at high concentrations compared to the parent mycotoxins. There are also several other metabolites that occur individually at low concentrations compared to the parent molecules, but may collectively contribute significantly to the overall type A trichothecene occurrence in cereals and cereal products. In recent studies using host plants inoculated with isotope-labelled mycotoxins, 70–85% of the inoculated T-2 or HT-2 was metabolized *(60–61)* (Annex 1, reference *247*).

At its ninetieth meeting, the Committee noted that T-2 and HT-2 usually co-occur in food commodities and finished products as they are both produced by the same *Fusarium* species through the same metabolic pathway (Annex 1, reference *247*). Additionally, the Committee observed that *Fusarium langsethiae* and *F. sporotrichioides* are capable of producing several other derivatives, such as NEO, T-2 triol and T-2 tetraol, DAS, monoacetoxyscirpenol (MAS) and scirpentriol (SCR). However, it noted that these trichothecenes are not commonly included in

mycotoxin surveys, but, where they are, they can be detected as co-contaminants with T-2 and HT-2, particularly where analytical methods with low LODs are used. These few studies are restricted to European cereals, where DAS is detected at low frequency and at low concentrations.

2.12 Food consumption and dietary exposure assessment

2.12.1 Acute dietary exposure

Three studies reported in the scientific literature estimated acute dietary exposure to T-2, HT-2 or the sum of T-2 and HT-2. Two of the studies were duplicate diet studies carried out in the Netherlands, while the third study, by EFSA, estimated acute dietary exposure for a range of European countries. The EFSA study estimated maximum UB 95th percentile acute dietary exposures to T-2, HT-2 and the sum of T-2 and HT-2 of 137, 165 and 170 ng/kg bw, respectively *(62)*. These estimates were for infant cohorts, with acute dietary exposure decreasing with increasing age. The duplicate diet studies estimated mean acute dietary exposure to the sum of T-2 and HT-2 for young children (8–12 months) of 40 ng/kg bw (range 10–160 ng/kg bw). For 128 adults, acute dietary exposure to the sum of T-2 and HT-2 was in the range not detected to 18.6 ng/kg bw.

The Committee did not present additional national estimates of acute dietary exposure (Annex 1, reference *247*).

2.12.2 Chronic dietary exposure

Since the previous evaluation, several national or regional estimates of chronic dietary exposure have been published. The Committee considered evaluations from Belgium, China, the Czech Republic, Ecuador, Europe, France, Ireland, Malawi, Morocco, the Netherlands, New Zealand, Nigeria, Pakistan, Romania, Serbia, Spain, Sweden, sub-Saharan Africa, Tunisia and the United Republic of Tanzania. These reports include dietary exposure assessments for T-2 (12 studies), HT-2 (14 studies) and the sum of T-2 and HT-2 (12 studies). In several studies, these toxins were not detected or were detected so infrequently that dietary exposure could not be estimated. Estimates of dietary exposure reviewed mainly related to European and north African countries. Table 2 provides a summary of the range of exposure estimates derived from the scientific literature. Exposure estimates have been further separated into those pertaining to children, including infants and toddlers and those pertaining to adults or the general population. Dietary exposure estimates have mostly been presented as ranges from an LB to an upper bound (UB). LB estimates are generally based on mean toxin concentrations calculated with results below the LOD or limit of quantitation (LOQ) being assigned a value of zero. UB estimates are generally based on mean toxin concentrations calculated with results below the LOD or LOQ being assigned a value equal to the LOD or LOQ.

Table 2
Summary of the range of estimates of chronic dietary exposure to T-2, HT-2 and the sum of T-2 and HT-2, derived from the literature

Toxin/population group[a]	Estimated dietary exposure, range[b] (ng/kg bw per day)			
	Mean		High percentile[c]	
	LB	UB	LB	UB
T-2				
Children	0.4–26	13–79	5.7[d]–150	27–200
Adults	0.1–6.4	9.1–24	1.6–29	16–66
HT-2				
Children	0.0–27	4.1–91	3.6–64	15–240
Adults	0.0–14	0.4–33	2.4–23	14–59
Sum of T-2 and HT-2				
Children	0.8–53	8.2–169	6.5–210	31–400
Adults	0.3–27	2.7–60	1.9–87	11–120

LB: lower bound, UB: upper bound.
[a] For the purpose of this summary table, "children" were taken to be any population group described as infants, toddlers or children. The maximum age for children varies from study to study, but in all cases "children" will refer to individuals aged 15 years or younger. "Adults" were taken to be any population group described as adults, adolescents, elderly or very elderly. The minimum age for adults varies from study to study, but in all cases "adults" will refer to individuals older than 10 years.
[b] Ranges are presented separately for lower and upper bound estimates of mean and high percentile estimates of dietary exposure.
[c] 95th percentile, unless otherwise indicated.
[d] 90th percentile.

Across studies, the foods providing the major contributions to chronic dietary exposure are cereals and cereal-based, particularly wheat and wheat-based, products.

Based on the observed geographical distribution of T-2 and HT-2 contamination of foods (mainly Europe and North America) and available food consumption information, the Committee, at its current [ninetieth] meeting, decided it was unnecessary to derive additional national estimates of chronic dietary exposure to T-2 and HT-2.

At the current [ninetieth] meeting, the Committee did not present international estimates of dietary exposure to either toxin or the sum of the toxins using the GEMS/Food cluster diets. It was concluded that dietary exposure to T-2 and HT-2 for clusters covering the known geographical distribution of T-2 and HT-2 was suitably covered by existing European estimates of chronic dietary exposure and no international estimates of chronic dietary exposure were derived by the Committee (Annex 1, reference *247*).

2.13 Combined dietary exposure to T-2, HT-2 and DAS

The present Committee re-evaluated the combined dietary exposure to T-2, HT-2 and DAS.

Owing to the high level of left-censorship in the dataset for DAS (up to 100% for some regions), which had heavily impacted the regional estimates of chronic dietary exposure to DAS estimated at the eighty-third meeting, a tiered approach to combined acute or chronic dietary exposure to T-2, HT-2 and DAS was taken at the current meeting by the Committee by initially considering LB estimates of dietary exposure. This would represent the best reliable actual combined dietary exposure scenario to T-2, HT-2 and DAS where, if LB estimates are less than the group acute reference dose (ARfD) or the group TDI, the more conservative UB combined estimates can be examined.

Acute dietary exposure to the sum of T-2 and HT-2 was previously evaluated by the Committee in 2020 (Annex 1 reference *247*). The highest UB (the LB approach was not reported in the EFSA report) 95th percentile exposure estimate of 170 ng/kg bw was reported for infants in European countries. It was also noted that the acute dietary exposure estimates decreased with increasing age. The Committee also noted that acute exposure to DAS was not evaluated at its eighty-third meeting, confirming that at the present meeting, the Committee was unable to carry out an assessment of combined acute dietary exposure to T-2, HT-2 and DAS due to insufficient information.

Chronic dietary exposure to the sum of T-2 and HT-2 was evaluated by the Committee at the present meeting. Based on the data reported in Table 2, and a review of the literature for the general population, LB estimates of mean exposure to the sum of T-2 and HT-2 are in the range of 0.3–53 ng/kg bw per day, while LB high percentile estimates of dietary exposure are in the range of 1.9–210 ng/kg bw per day. At the eighty-third meeting of the Committee, regional estimates of chronic dietary exposure to DAS were estimated: LB mean estimates were in the range of 0.0–2.8 ng/kg bw per day and LB high percentile (90th) estimates were in the range of 0.0–5.6 ng/kg bw per day.

Combined acute or chronic estimates of dietary exposure to T-2, HT-2 and DAS from different studies, regions and population groups should only be made with a high level of caution. The Committee noted that only LB estimates of chronic dietary exposure to DAS were available and these estimates were much lower than the estimates of combined dietary exposure to T-2 and HT-2. For this reason, a first-tier approach of considering the risks associated with combined acute or chronic dietary exposure to only the sum of T-2 and HT-2 was adopted.

2.14 Dose–response analysis

The Committee determined that effects on feed intake, body weight and immunological and haematological end-points are sensitive measures of T-2-induced toxicity. For the purposes of establishing an ARfD and a group TDI,

dose–response analysis was conducted on selected effects observed following acute and repeated dose oral exposure.

2.14.1 Acute toxicity

For acute toxicity, the Committee reviewed the study in mink by Wu et al. (2016), which showed that exposure to T-2 and HT-2 significantly increased incidence of emesis in a dose-responsive fashion at doses ≥ 50 µg/kg bw following both single gavage and intraperitoneal exposure. Notably, the emetic effects of T-2 and HT-2 in mink were accompanied by similar biochemical changes (for example, alterations in various anorexigenic hormones) to those that occurred with the T-2- and HT-2-induced effects on feed intake in mice (*17–19*). For modelling purposes, the incidences of emesis in mink for T-2 and HT-2 reported in Wu et al. *(16)* were pooled and are summarized in Table 3.

Considering the potential additive effects of exposure to T-2, HT-2 and DAS (Annex 1 reference *235)*, the Committee conducted dose–response modelling of the emetic effects of DAS in mink following acute oral exposure. This analysis was used to compare the emetic potencies of DAS, T-2 and HT-2. Table 4 summarizes the incidence of emesis in mink reported by Wu et al. *(47)* following acute gavage exposure to DAS.

Modelling was carried out for the induction of emesis in mink by acute oral exposure to T-2 and HT-2, using ToxicR, version 22.01 (1.0.0). As recommended in the recent WHO/IPCS (2020) Chapter 5 update *(3)* on dose–response modelling, model average estimates were computed. Benchmark dose analyses were conducted using the extra risk for quantal data with the benchmark response set to 10%. A benchmark response of 10% is the standard/default value for quantal data *(3)* and was considered appropriate by the Committee for the critical end-point. For relative potency considerations, similar data for DAS (i.e. *(47)*) were modelled using the same modelling considerations as used for T-2 and HT-2. The results of this analysis are summarized in Table 5.

Based on the information in Table 5, the Committee selected the $BMDL_{10}$ of 2.6 µg/kg bw as the point of departure for T-2 and HT-2 and identified a relative potency factor of 0.2 for DAS.

2.14.2 Repeated-dose toxicity

The Committee focused the dose–response analysis on the juvenile pig study by Rafai et al. *(31)* because it investigated more than one treatment level at doses lower than the previously identified LOAEL of 29 µg/kg bw per day (Annex 1, reference *152*), and because accurate dose estimates could be derived and background mycotoxin contamination of the basal feed was characterized. Table 6 summarizes the data that were considered in the dose–response assessment.

Table 3
Pooled incidence of emesis in mink from oral gavage exposure to T-2 and HT-2 as reported by Wu et al. *(16)*

Dose	Number of animals	Incidence
0	4	0
0.005 mg/kg bw HT-2	4	0
0.005 mg/kg bw T-2	4	0
0.05 mg/kg bw HT-2	4	3
0.05 mg/kg bw T-2	4	3
0.25 mg/kg bw HT-2	4	4
0.25 mg/kg bw T-2	4	4
0.5 mg/kg bw HT-2	4	4
0.5 mg/kg bw T-2	4	4

Table 4
Incidence of emesis in mink from oral gavage exposure to DAS as reported by Wu et al. *(47)*

Dose (mg/kg bw)	Number of animals	Incidence
0	5	0
0.01	5	0
0.025	5	0
0.05	5	0
0.1	5	4
0.25	5	5

Table 5
Dose–response summary statistics for the emetic response in mink following acute gavage exposure to T-2/HT-2 or DAS

	BMD distribution (µg/kg bw)			
Trichothecene (study)	BMD_{10}	$BMDL_{10}$	$BMDU_{10}$	$BMD_{10}/BMDL_{10}$
T-2/HT-2 (Wu et al., 2016) *(16)*	8.6	2.6	24.1	3
DAS (Wu et al., 2020) *(47)*	36.8	14.4	65.2	3

BMD_{10}, benchmark dose for a 10% response; $BMDL_{10}$, lower 95% confidence limit on the benchmark dose for a 10% response; $BMDU_{10}$, upper 95% confidence limit on the benchmark dose for a 10% response; DAS, 4,15-diacetoxyscirpenol.

Concerning the immunological effects of T-2 exposure, the Committee noted the WHO/IPCS (2012) guidance *(63)* on immunotoxicity risk assessment for chemicals, which recommends that functional measures of the immune system be used for hazard characterization rather than observational end-

Table 6
Summary of selected effects in juvenile pigs reported by Rafai et al. (2013) *(31)*

	Dose (µg/kg bw per day)		
Effect	**0**	**11.2**	**18**
Terminal body weight (kg)	23.8±1	21.5±1*	20±0.88*
Daily body weight gain (weeks 1–3; g/day)	497±63	377±67*	317±96*
Feed intake (weeks 1–3; g/day)	889±99	694±136*	644±98*

n=10 animals per dose; means presented ± standard deviation; see Appendix for detailed dose calculations
* $P \leq 0.05$.

points (for example, leukocyte count). Since Rafai et al. *(31)* concluded that the T-cell-dependent antibody response was not observed at doses of either 11.2 or 18 µg/kg bw per day, the Committee focused its dose–response assessment on reduced body weight, daily body weight gain and feed intake. The Committee also expressed concerns about the reliability and reproducibility of the functional immune parameters measured in the key studies summarized previously, and the potential for decreased feed intake to affect the immunological and haematological parameters (Annex 1, reference *152*; *21–25*).

Modelling was carried out with ToxicR, version 22.01 (1.0.0) using a relative deviation approach. Ideally, a benchmark response (BMR) is set numerically so that it reflects the onset of a human-relevant adverse effect. The Committee considered a reduction in body weight gain in rapidly growing animals as an adverse effect but found it difficult to decide on a minimal level of adversity for such a reduction. In line with the updated Chapter 5 of EHC 240 guidance for such a situation *(3)*, the Committee chose to consider a range of BMRs, in this case, 5% or 10%, and give specific consideration to the corresponding BMD credible intervals (BMDL-BMDU interval) when selecting the point of departure and deciding on the numerical value of uncertainty factors for establishing the HBGV. The results of the modelling are summarized in Tables 7 and 8.

In the critical study by Rafai et al. *(31)*, animals were administered doses of 11.2 and 18 µg/kg body weight per day. Using this data with a BMR of 5%, the BMD_{05} and $BMDL_{05}$ are considerably below the lowest tested dose of 11.2 µg/kg body weight per day. Consequently, the calculation of the BMD is dependent on an extrapolation between 0 and 11.2, and this is true even if model averaging is used. As a result, there is increased statistical uncertainty when calculating the BMDL for low BMRs. For example, when considering daily body weight gain, the BMDL is 1.8 versus 0.6 µg/kg bw per day for BMRs of 10 and 5%, respectively. This calculation represents a threefold decrease in the BMDL, corresponding to a halving of the BMR, which implies increased heterogeneity (at doses below the

Table 7

Dose–response summary statistics for the critical effects in juvenile pigs following short-term dietary exposure to T-2 (Rafai et al., 2013) *(31)* using a benchmark response of 5%

	BMD distribution (µg/kg bw per day)			
End-point	**BMD_{05}**	**$BMDL_{05}$**	**$BMDU_{05}$**	**$BMD_{05}/BMDL_{05}$**
Terminal body weight (day 21)	6.4	3.6	9.0	2
Daily body weight gain (weeks 1 to 3)	2.9	0.6	6.2	5
Daily feed intake (weeks 1 to 3)	2.7	0.2	6.3	14

BMD_{05}, benchmark dose for a 5% response; $BMDL_{05}$, lower 95% confidence limit on the benchmark dose for a 5% response; $BMDU_{05}$, upper 95% confidence limit on the benchmark dose for a 5% response.

Table 8

Dose–response summary statistics for the critical effects in juvenile pigs following short-term dietary exposure to T-2 (Rafai et al., 2013) *(31)* using a benchmark response of 10%

	BMD distribution (µg/kg bw per day)			
End-point	**BMD_{10}**	**$BMDL_{10}$**	**$BMDU_{10}$**	**$BMD_{10}/BMDL_{10}$**
Terminal body weight (day 21)	11.6	8.8	14.2	1
Daily body weight gain (weeks 1 to 3)	5.4	1.8	9.1	3
Daily feed intake (weeks 1 to 3)	5.6	0.7	9.9	8

BMD_{10}, benchmark dose for a 10% response; $BMDL_{10}$, lower 95% confidence limit on the benchmark dose for a 10% response; $BMDU_{10}$, upper 95% confidence limit on the benchmark dose for a 10% response.

observed range). For all the reasons stated above, the Committee decided that computing the BMD at a 10% BMR was appropriate.

Considering the uncertainties inherent in measuring feed intake of animals that were housed in groups and the larger model uncertainty associated with the corresponding BMD estimates, the Committee selected the $BMDL_{10}$ of 1.8 µg/kg bw per day based on reduced daily body weight gain for hazard characterization purposes.

2.15 Evaluation

At its ninetieth meeting, the Committee (Annex 1, reference *247*) reviewed the information that had become available since 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.

T-2 exposure induces emesis, reduced feed intake, reduced body weight gain, immunotoxicity and haematotoxicity following acute and short-term intake in multiple species. 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 (Annex 1, reference *235*), 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 *(47)*. 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 LODs are used.

Although the effects and proposed mechanisms elicited by other trichothecenes (NEO, DON, 3-ADON, 15-ADON, FUS-X and NIV) 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.

2.15.1 Group ARfD

Emesis is a common effect of acute trichothecene exposure in both humans and experimental animals (Annex 1, references *152*, *200*, *235*). On this basis, the Committee established a group ARfD for T-2, HT-2 and DAS using the $BMDL_{10}$ 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[1]) 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 the CNS).
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 C_{max} rather than area under the concentration–time curve.

[1] See EHC 240 *(3)*.

3) The point of departure is based on a gavage study where higher C_{max} concentrations 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 (*47*). Furthermore, like T-2 and HT-2, DAS has induced reduced feed intake in mice via a similar mode of action *(45, 46)*.

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 by Wu et al. *(16)* and Wu et al. *(47)* 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 DAS exposure.

2.15.2 Group 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 by Rafai et al. *(31)*. 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 sensitive species to the emetic and haematotoxic effects of trichothecenes *(64, 65)*. Dose–response analysis of body weights, daily body weight gain and daily feed intake reported by Rafai et al. *(31)* was conducted and a $BMDL_{10}$ 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 an HBGV.

Considering that the critical effect (i.e. nausea-induced reductions in feed intake resulting in decreased body weight gain) is likely to be C_{max}-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 ARfD; 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 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 DAS and T-2 and HT-2 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.

2.15.3 Risk characterization

2.15.3.1 Acute dietary exposure

Acute dietary exposure to the sum of T-2 and HT-2 was previously evaluated by the Committee in 2020 (Annex 1, reference *247*). The highest 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 at its eighty-third meeting, acute exposure to DAS was not evaluated.

There is insufficient information available to estimate combined acute exposure to T-2, HT-2 and DAS. The dietary exposure estimates made by the Committee for T-2 and HT-2 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.

2.15.3.2 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 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.

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3. Recommendations

The Committee recommended the following:

1) Development of analytical multimycotoxin 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 mycotoxin mixtures (for example, those that co-occur).

A monograph addendum was prepared.

Appendix

Dose calculations

Rafai et al., 1995a,b					
Week 1					
Diet (mg/kg diet)	**Initial mean body weight (kg)**	**Mean daily weight gain (g/day)**	**Body weight (kg)**	**Mean daily feed intake (g/day)**	**Dose (µg/kg bw per day)**
0	9.3	404.6	12.13	630.7	0
0.5	9.1	291.4	11.14	565.4	25
1	9.4	354.1	11.88	644.8	54
2	8.6	223.9	10.17	471.3	93
3	8.7	146.1	9.72	401.7	124
Week 2					
0	12.13	451.4	15.29	845.1	0
0.5	11.14	387.1	13.85	704.6	25
1	11.88	487.3	15.29	923.7	60
2	10.17	348.6	12.61	727.6	115
3	9.72	280	11.68	512	131
Week 3					
0	15.29	534.3	19.03	976	0
0.5	13.85	505.7	17.39	872.9	25
1	15.29	490.5	18.72	751.5	40
2	12.61	382.9	15.29	765.6	100
3	11.68	240	13.36	533.8	120

Estimated doses and conversion factors		
Diet (mg/kg diet)	**Average doses weeks–13 (µg/kg bw per day)**	**Conversion factors**
0.5	**25**	50.6 µg/kg bw per day per mg/kg diet
1	**52**	51.6 µg/kg bw per day per mg/kg diet
2	**103**	51.4 µg/kg bw per day per mg/kg diet
3	**125**	41.7 µg/kg bw per day per mg/kg diet

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Week 1				
Diet (mg/kg diet)	**Initial mean body weight (kg)**	**Day 7 mean body weight (kg)**	**Mean daily feed intake (kg)**	**Dose (µg/kg bw per day)**
0	13.4	16.9	0.774	0.0
0.3	13.6	15.9	0.571	10.8
0.5	13.3	16	0.608	19.0
Diet (mg/kg diet)	**Initial mean body weight (kg)**	**Day 14 mean body weight (kg)**	**Mean daily feed intake (kg)**	**Dose (µg/kg bw per day)**
Week 2				
0	13.4	20.4	0.919	0.0
0.3	13.6	18.3	0.649	10.6
0.5	13.3	17.6	0.574	16.3

Week 3				
Diet (mg/kg diet)	Initial mean body weight (kg)	Day 21 mean body weight (kg)	Mean daily feed intake (kg)	Dose (µg/kg bw per day)
0	13.4	23.8	0.973	0.0
0.3	13.6	21.5	0.863	12.0
0.5	13.3	20	0.75	18.8

Estimated doses and conversion factors		
Diet (mg/kg diet)	Average doses weeks 1–3 (µg/kg bw per day)	Conversion factors
0.3	**11.2**	37.2 µg/kg bw per day per mg/kg diet
0.5	**18.0**	36.0 µg/kg bw per day per mg/kg diet

Annex 1

Reports and other documents resulting from previous meetings of the Joint FAO/WHO Expert Committee on Food Additives

1. General principles governing the use of food additives (First report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).

2. Procedures for the testing of intentional food additives to establish their safety for use (Second report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).

3. Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants) (Third report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. I. Antimicrobial preservatives and antioxidants, Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).

4. Specifications for identity and purity of food additives (food colours) (Fourth report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as Specifications for identity and purity of food additives, Vol. II. Food colours, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).

5. Evaluation of the carcinogenic hazards of food additives (Fifth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).

6. Evaluation of the toxicity of a number of antimicrobials and antioxidants (Sixth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962 (out of print).

7. Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents (Seventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).

8. Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants (Eighth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 38, 1965; WHO Technical Report Series, No. 309, 1965 (out of print).

9. Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants. FAO Nutrition Meetings Report Series, No. 38A, 1965; WHO/Food Add/24.65 (out of print).

10. Specifications for identity and purity and toxicological evaluation of food colours. FAO Nutrition Meetings Report Series, No. 38B, 1966; WHO/Food Add/66.25.

11. Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases (Ninth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).

12. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases. FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29.

13. Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances (Tenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.

14. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents (Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.

15. Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.

16. Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents. FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.

17. Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics (Twelfth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.

18. Specifications for the identity and purity of some antibiotics. FAO Nutrition Meetings Series, No. 45A, 1969; WHO/Food Add/69.34.

19. Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances (Thirteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.

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21. Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives. FAO Nutrition Meetings Report Series, No. 46B, 1970; WHO/Food Add/70.37.

22. Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents (Fourteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 48, 1971; WHO Technical Report Series, No. 462, 1971.

23. Toxicological evaluation of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.

24. Specifications for the identity and purity of some extraction solvents and certain other substances. FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.

25. A review of the technological efficacy of some antimicrobial agents. FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.

26. Evaluation of food additives: some enzymes, modified starches, and certain other substances: Toxicological evaluations and specifications and a review of the technological efficacy of some

antioxidants (Fifteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.

27. Toxicological evaluation of some enzymes, modified starches, and certain other substances. FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.

28. Specifications for the identity and purity of some enzymes and certain other substances. FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.

29. A review of the technological efficacy of some antioxidants and synergists. FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.

30. Evaluation of certain food additives and the contaminants mercury, lead, and cadmium (Sixteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.

31. Evaluation of mercury, lead, cadmium and the food additives amaranth, diethylpyrocarbamate, and octyl gallate. FAO Nutrition Meetings Report Series, No. 51A, 1972; WHO Food Additives Series, No. 4, 1972.

32. Toxicological evaluation of certain food additives with a review of general principles and of specifications (Seventeenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum (out of print).

33. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents. FAO Nutrition Meetings Report Series, No. 53A, 1974; WHO Food Additives Series, No. 5, 1974.

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35. Evaluation of certain food additives (Eighteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 54, 1974; WHO Technical Report Series, No. 557, 1974, and corrigendum.

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89. Toxicological evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 26, 1990.

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194. Toxicological evaluation of certain veterinary drug residues in food. WHO Food Additives Series, No. 61, 2009.

195. Residue evaluation of certain veterinary drugs. FAO JECFA Monographs 6, 2009.

196. Evaluation of certain food additives (Seventy-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 956, 2010.

197. Safety evaluation of certain food additives. WHO Food Additives Series, No. 62, 2010.

198. Compendium of food additive specifications. FAO JECFA Monographs 7, 2009.

199. Evaluation of certain contaminants in food (Seventy-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 959, 2011.

200. Safety evaluation of certain contaminants in food. WHO Food Additives Series, No. 63/FAO JECFA Monographs 8, 2011.

201. Residue evaluation of certain veterinary drugs. FAO JECFA Monographs 9, 2010.

202. Evaluation of certain food additives and contaminants (Seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 960, 2011.

203. Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 64, 2011.

204. Compendium of food additive specifications. FAO JECFA Monographs 10, 2010.

205. Evaluation of certain food additives and contaminants (Seventy-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 966, 2011.

206. Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 65, 2011.

207. Compendium of food additive specifications. FAO JECFA Monographs 11, 2011.

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217. Evaluation of certain veterinary drug residues in food (Seventy-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 988, 2014.

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222. Compendium of food additive specifications. FAO JECFA Monographs 16, 2014.

223. Evaluation of certain food additives and contaminants (Eightieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 995, 2016.

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228. Residue evaluation of certain veterinary drugs. FAO JECFA Monographs 18, 2016.

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230. Evaluation of certain food additives (Eighty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 1000, 2016.

231. Compendium of food additive specifications. FAO JECFA Monographs 19, 2016.

232. Safety evaluation of certain food additives. WHO Food Additives Series, No. 73, 2017.

233. Evaluation of certain contaminants in food (Eighty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 1002, 2017.

234. Evaluation of certain food additives (Eighty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 1007, 2017.

235. Safety evaluation of certain contaminants in food. WHO Food Additives Series, No. 74, FAO JECFA Monographs 19 bis, 2018.

236. Compendium of food additive specifications. FAO JECFA Monographs 20, 2017.

237. Safety evaluation of certain food additives. WHO Food Additives Series, No. 75, 2019.

238. Evaluation of certain veterinary drug residues in food (Eighty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 1008, 2018.

239. Residue evaluation of certain veterinary drugs. FAO JECFA Monographs 21, 2018.

240. Compendium of food additive specifications. FAO JECFA Monographs 22, 2018.

241. Toxicological evaluation of certain veterinary drug residues in food. WHO Food Additives Series, No. 76, 2019.

242. Evaluation of certain food additives (Eighty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 1014, 2019.

243. Evaluation of certain food additives (Eighty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, No. 1020, 2019.

244. Evaluation of veterinary drug residues in food (Eighty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, No. 1023, 2020.

245. Evaluation of certain food additives (Eighty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, No. 1027, 2021.

246. Safety evaluation of certain food additives. WHO Food Additives Series, No. 80, 2022.

247. Evaluation of certain contaminants in food (Ninetieth report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, No. 1032, 2022.

Annex 2

Toxicological and dietary exposure information and conclusions

Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Ninety-third meeting
Virtual meeting, 24, 25, 29, 30 March and 1 April 2022

SUMMARY AND CONCLUSIONS
Issued on 12 April 2022

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 summarizes 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.

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:
http://www.fao.org/food-safety/scientific-advice/jecfa/en/
and
https://www.who.int/foodsafety/en/

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 (Cmax) rather than area under the concentration–time curve.

Review of toxicological data on the trichothecenes T-2, HT-2 and DAS and re-evaluation of the combined dietary exposure	
	3. The point of departure is based on a gavage study where higher Cmax 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 ARfD; 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[5]) 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.

[5] "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).

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

Meeting agenda

Food and Agriculture Organization of the United Nations

World Health Organization

93rd JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)
24, 25, 29, 30 March and 1 April 2022

Virtual meeting: 12 pm – 3 pm (Geneva time)

1. Opening
2. Declarations of Interests (information by the Secretariat on any declared interests and discussion, update by experts)
3. Election of Chairperson and Vice-Chairperson, appointment of Rapporteurs
4. Adoption of the agenda
5. Matters of interest arising from previous Sessions of the Codex Committee on Contaminants in Food (CCCF)
6. Critical issues and questions from Working Papers (first brief round of discussion on all subjects to inform the full Committee)
7. Evaluations

   7.1. Trichothecenes (T2 and HT2)

8. Other matters to be considered (general considerations).
9. 9. Other matters brought forward by the Committee during discussions at the meeting.
10. Adoption of the report.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

Evaluation of certain contaminants in food
Ninetieth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1032, 2022 (144 pages)

Evaluation of certain food additives
Eighty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1027, 2020 (106 pages)

Evaluation of certain veterinary drug residues in food
Eighty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1023, 2020 (116 pages)

Evaluation of certain food additives
Eighty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1020, 2019 (109 pages)

Evaluation of certain food additives
Eighty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1014, 2019 (156 pages)

Evaluation of certain veterinary drug residues in food
Eighty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1008, 2017 (150 pages)

Safety evaluation of certain food additives
Eighty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives
WHO Food Additives Series, No. 75, 2018 (244 pages)

Evaluation of certain food additives
Eighty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives
WHO Technical Report Series, No. 1007, 2017 (92 pages)

Safety evaluation of certain contaminants in food
Eighty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives
WHO Food Additives Series, No. 74, 2018 (897 pages)

Further information on these and other WHO publications can be obtained from
WHO Press, World Health Organization ▪ 1211 Geneva 27, Switzerland ▪ www.who.int/bookorders
tel.: +41 22 791 3264; **fax:** +41 22 791 4857; **email:** bookorders@who.int

Evaluation of certain contaminants in food

This report represents the conclusions of a Joint FAO/WHO Expert Committee convened to evaluate the toxicological data on T-2 and HT-2 and the combined dietary exposure was re-evaluated. At its ninetieth meeting, JECFA had 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 report summarizes the main conclusions of the Committee regarding the group acute reference dose and tolerable daily intake for T-2, HT-2 and DAS, as well as the risk characterization and recommendations.

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