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Scientific Committee on Food

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**Opinion of the Scientific Committee on Food on *Fusarium* toxins.
Part 6: Group evaluation of T-2 toxin, HT-2 toxin, nivalenol and
deoxynivalenol**

(adopted on 26 February 2002)

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Terms of reference

Although it is acknowledged that there are gaps in the toxicological information available, the Scientific Committee on Food is requested

- to assess the health risk associated with exposure to the different *Fusarium* toxins in cereals, taking into the account the current state of knowledge.
- to indicate, on the basis of current knowledge, which of these *Fusarium* toxins are of most concern for public health and for which there is an urgent need for further research and/or need for measures to reduce the presence of these toxins in cereals.
- to indicate, if possible, the nature of the toxicological studies to recommend in order to elucidate (more) completely the toxicology of these toxins.

In considering these issues the Committee is asked to take note, inter alia, of the comprehensive report “*Fusarium* toxins in cereals – a risk assessment” which has been prepared for the Nordic Council of Ministers.

Background

A variety of *Fusarium* fungi, which are common soil fungi, produce a number of different mycotoxins of the class of trichothecenes (T-2 toxin, HT-2 toxin, deoxynivalenol (DON) and nivalenol) and some other toxins (zearalenone and fumonisins). The *Fusarium* fungi are probably the most prevalent toxin-producing fungi of the northern temperate regions and are commonly found on cereals grown in the temperate regions of America, Europe and Asia. Most of the toxin producing *Fusarium* species are capable of producing to a variable degree two or more of these and other toxins (Eriksen and Alexander, 1998).

Fusarium toxins have been shown to cause a variety of toxic effects in both experimental animals and livestock. On some occasions toxins produced by *Fusarium* species have also been suspected to cause toxicity in humans.

In a set of Opinions the Committee evaluated the *Fusarium* toxins: deoxynivalenol (DON) (SCF, 2 December 1999), zearalenone (SCF, 22 June 2000), fumonisin B1 (SCF, 17 October 2000), nivalenol (SCF, 19 October 2000) and T-2 toxin and HT-2 toxin (SCF, 30 May 2001).

For the trichothecenes (DON, nivalenol, T-2 toxin and HT-2 toxin) the Committee established temporary TDIs pending, among other things, a group evaluation since these toxins belong to a group of several toxins with a common basic chemical structure and because most of the *Fusarium* species are capable of producing several trichothecenes. For T-2 toxin and HT-2 toxin a group t-TDI was already established because the acute toxicity of T-2 toxin and HT-2 toxin are within the same range, T-2 toxin is rapidly metabolised to HT-2 toxin *in vivo* and the toxicity of T-2 toxin at least partly could be attributed to HT-2 toxin.

Introduction

In the framework of the terms of reference taking into account the opinion on the individual trichothecenes expressed by the Committee, the objective of the present opinion is to evaluate whether the establishment of a group TDI for the four trichothecenes is appropriate and if so, the feasibility of doing so.

The establishment of a group TDI for several compounds should be considered when they share a common mode of action and there is frequent co-exposure. In such cases a given combined exposure to several compounds, may exceed the threshold dose for effect, although the exposure for each single compound is below their respective No Observed Adverse Effect Levels (NOAELs). In the case of the trichothecenes, which are discussed in this document, combined exposure could be regarded as simple mixture according to a recent paper discussing how to evaluate the toxicology of simple and complex mixtures (Groten *et al.*, 2001). The Committee chose to use the terminology of Groten *et al.* (2001) to describe the resulting effect of a combined exposure and classified these as one of three types of combined effects: 1. Effect additivity (dissimilar mode of action or independent action), 2. Dose additivity (similar mode of action) and 3. Deviation from additivity (synergism or antagonism).

Effect additivity: there is no need for a group TDI because the toxicity of one compound is exerted independently from the toxicity of another compound, even if they act on the same target organ. This means that when the doses of the chemicals are below the no-effect levels of the individual compounds, i.e. the effect of each chemical equals zero, the combined action of all chemicals together will also be zero.

Dose additivity: a group TDI is justified. However, this requires that there is a common mechanism of action and an addition of the dose from several compounds at the molecular target resulting in an effect even if the dose of each single compound is below the threshold dose for effect. A typical example of the use of a dose additivity model in risk assessment is in the case of polychlorinated di-benzo-*p*-dioxins and “dioxin-like compounds” where the toxicity is assumed to be mediated via a common target, the Ah-receptor (SCF, 2001b). In the case of dose additivity the construction of a group TDI requires the knowledge of the potency of the single compounds in question.

Deviation from additivity: the combined effect may be increased, i.e. synergism or decreased, i.e. antagonism. In this case, particularly when synergism is observed, a group TDI is also justified.

The Committee noted that the nature of the combined effects might depend on the dose, especially in the case of deviation from additivity. Hence, when there is a deviation from additivity any group TDI should not be established from data generated by using overtly toxic doses because this may produce (false) interactions that are of no relevance for the human exposure situation.

Chemistry

The trichothecenes are tetracyclic sesquiterpenoid compounds with a 12,13-epoxy group. Those produced by *Fusarium* species belong to two categories according to functional groups. T-2 toxin and HT-2 toxin belong to group A, which is characterised by a functional group other than a carbonyl at C-8. Trichothecenes with a carbonyl group at C-8 belong to group B. Deoxynivalenol (DON) and nivalenol belongs to the latter group (Eriksen and Alexander, 1998).

Biochemical and cellular effects and potential modes of action

The most prominent common effects of T-2 toxin, HT-2 toxin, DON and nivalenol at the biochemical and cellular level are:

- the strong inhibitory effect on the protein synthesis by binding to the ribosomes,
- the inhibitory effect on RNA and DNA synthesis and
- toxic effects on cell membranes.

Another common effect is the induction of apoptosis particularly in lymphatic and haematopoietic tissue (Eriksen and Alexander, 1998; SCF, 1999, 2000c, 2001a). It appears that different trichothecenes differ in their capacity to inhibit protein synthesis, to activate the mitogen activated protein kinases (MAP kinases) and to induce apoptosis (Shifrin and Anderson, 1999; Yang *et al.*, 2000). It is not clear whether the toxins work via identical mechanisms at the biochemical and cellular level.

Toxic effects

For T-2 toxin, HT-2 toxin, DON and nivalenol the general toxicity and immunotoxicity are considered to be the critical effects (Eriksen and Alexander, 1998; SCF, 1999, 2000c, 2001a). Regarding myelotoxic effects T-2 toxin is the most potent both *in vivo* and *in vitro*, whereas DON shows no cytotoxicity towards erythroblast progenitors and weak toxicity towards granulocyte /monocyte progenitor cells *in vitro* (Parent-Massin and Parchment, 1998). A special feature of DON toxicity is the characteristic induction of vomiting (DON is also called vomitoxin) and feed refusal seen in pigs or delayed gastric emptying and feed refusal observed in rats and mice. The emetic effect is thought to be mediated by affecting serotonergic activity in the central nervous system (CNS) or via peripheral actions on serotonin receptors (SCF, 1999).

Table 1. Critical effects of trichothecenes

Compound	Critical effects LOAEL/NOAEL (mg/kg bw/day)			
	Growth retardation*	Leukopenia/ reduced antibody production	Reproductive effects	Increased susceptibility to infections
Nivalenol	0.7 (LOAEL)** Mouse, 1 and 2 years (Ohtsubo <i>et al.</i> , 1989; Ryu <i>et al.</i> , 1988)	0.7 (LOAEL) Mouse, 1 and 2 years (Ohtsubo <i>et al.</i> , 1989; Ryu <i>et al.</i> , 1988)	1.4 (LOAEL) Intrauterin growth retardation Mouse through gestation (Ito <i>et al.</i> , 1988 (in Japanese), cit. WHO, 1990)	
DON	0.1 (NOAEL) Mouse (Iverson <i>et al.</i> , 1995)		0.375 (NOAEL) Mouse, increased postnatal mortality (Khera <i>et al.</i> , 1984)	0.25 (NOAEL) Mouse (Tryphonas <i>et al.</i> , 1986)
T-2 toxin (HT-2 toxin)	0.04 (LOAEL) Pig, 8 weeks Reduced body weight gain (Weaver <i>et al.</i> , 1978)	0.03 (LOAEL) Pig, 3 weeks (subacute) (Rafai <i>et al.</i> , 1995)	0.45 (NOAEL) Embryo- or foetotoxicity Mouse, CD-1, two generations. No dose showing effect. (Rousseaux <i>et al.</i> , 1986)	

* It should be noted that growth retardation is a very unspecific effect for these toxins which may be due to effects on the central nervous system, reduced feed consumption or other toxic parameters.

** LOAELs/NOAELs presented in bold were used in the derivation of the t-TDIs.

Critical effects identified for T-2 toxin, HT-2 toxin, DON and nivalenol including those used as basis for the derivation of tolerable intakes are listed in table 1. These effects are growth retardation, leukopenia/ reduced antibody production, reproductive effects and increased susceptibility to infections. All the toxins affected the immune system. Similarly, growth retardation and reproductive effects are common for all these toxins. These effects are signs of

organ toxicity or general toxicity in the young/adult animal and in the foetus and can in theory occur via several mechanisms. Although one might hypothesise that common mechanisms could be inhibition of protein synthesis and triggering of apoptosis in different tissues, this has not been shown for all these toxins.

Studies on combined effects

There are a few studies addressing the effects of combined exposure to several trichothecenes.

In vitro

Thompson and Wannemacher (1986) examined the ability of nineteen trichothecenes to inhibit protein synthesis in Vero cells and rat spleen lymphocytes. The lymphocytes were more sensitive than the Vero cells, but a good correlation was found between the two cell systems. Some toxins (T-2 toxin, diacetoxyscirpenol, DON and verrucarins-A) were also tested in a combination of 2, 3 and 4 of the toxins for protein synthesis inhibition in Vero cells. Dose additivity was observed for some of the toxins tested. However, DON, which is hundred fold less potent than T-2 toxin with respect to protein synthesis inhibition, appeared to be slightly antagonistic in an equimolar combination with T-2 toxin. No synergistic action was noted.

The relative potencies of the trichothecenes with respect to protein synthesis inhibition in Vero cells were also compared to lethality in mice (Thompson and Wannemacher, 1986). Several trichothecenes were relatively weak inhibitors of protein synthesis *in vitro* (e.g. nivalenol), but were much more potent *in vivo* in regard of their acute toxicity. No testing of combined exposure was performed *in vivo*.

Thuvander and co-workers (1999) examined the inhibitory effect of combined exposure to several trichothecenes on the proliferation of human peripheral lymphocytes stimulated with phytohaemagglutinin or pokeweed *in vitro*. Combinations of nivalenol with diacetoxyscirpenol (DAS), DON or T-2 toxin resulted in additive effects. There were no synergistic effects. Combinations of DON with T-2 toxin or DAS resulted in a toxicity that was significantly lower than, or similar to, the toxicity produced when exposed to T-2 toxin or DAS alone indicating an antagonistic effect.

The toxicity and interaction between trichothecenes has been studied in a yeast (*Kluyveromyces marxianus*) bioassay with inhibition of cell growth as the end point (Madhyastha *et al.*, 1994). Combinations of T-2 toxin and HT-2 toxin, T-2 toxin and T2-tetrol, DON and nivalenol, or DON and T2 were tested. T-2 toxin and HT-2 toxin and also DON and nivalenol in combination exhibited apparent synergism, whereas a combination of DON and T-2 toxin showed antagonistic responses. In another study Koshinsky and Khachatourians (1992) tested combinations of T-2 toxin and HT-2 toxin and found that the combined effect changed from antagonistic to synergistic at a low and high percent of

inhibition, respectively. The underlying mechanisms of growth inhibition are not known and the relevance of this assay for human health is uncertain.

In vivo

Rotter and co-workers (1992) exposed growing pigs for 2 and 3 weeks to feed containing 2 mg/kg feed of one of several *Fusarium graminearum* metabolites: sambucinol, 15 acetyl deoxynivalenol, 3-acetyldeoxynivalenol, culmorin and dihydroxycalonectrin, with and without 6 mg DON/kg feed. All the metabolites were isolated from the media of large-scale cultures of *Fusarium*. Reduced feed consumption and weight gain when DON was present in the feed were the only significant effects seen. No significant combined effects between DON and the other trichothecenes were noted.

Friend and co-workers (1992) fed twelve weeks old pigs feed containing 0.1, 0.4, 0.8, 1.6 or 3.2 mg T-2 toxin/kg feed with and without 2.5 mg DON/kg feed for five weeks. The sources of T-2 toxin and DON were: T-2, *Fusarium sporotrichioides* grown on solid substrate rice and containing less than 0.04 % HT-2 toxin and DON, *Fusarium graminearum* Schwabe DAOM 180377. These cultures were mixed in the feed. A reduced feed consumption was observed in the group fed the highest level of T-2 toxin and a non-significant trend in reduced body weight gain with increasing concentration of T-2 toxin was also observed. DON alone caused a significant reduction in both feed intake and body weight gain. Upon combined exposure to T-2 toxin and DON a reduced feed intake and body weight gain were observed at the lowest and the highest dose of T-2 toxin, while there was little effect on the intermediate T-2 toxin dose. The necropsy data showed increased macroscopic scores of toxicity in the stomach mucosa in pigs exposed to DON alone. Such changes were not observed for T-2 toxin alone. Generally, T-2 toxin did not cause changes in clinical chemistry or haematological values. The authors stated, without presenting any data, that some effects on clinical chemistry or haematological parameters could be attributed to DON and combined exposure to DON and T-2 toxin.

The individual and combined toxicity of DON and T-2 toxin was examined in broiler chicks (Kubena *et al.*, 1989). The chicks were exposed to non-contaminated wheat or wheat naturally contaminated with DON (16 mg/kg feed) with and without pure T-2 toxin added to the feed (4 mg/kg). The toxins significantly reduced final body weights and total body weight gains upon combined exposure, but not when given singly. The incidence and severity of oral lesions induced by T-2 toxin were only slightly, but not significantly increased by the combined exposure. Some haematological and clinical chemistry parameters, i.e. mean corpuscular volume, total protein, albumin, cholesterol and lactate dehydrogenase (LDH) were also determined. There was a decrease in mean corpuscular volume in chicks fed DON singly or in combination with T-2 toxin. A significant reduction in serum total protein, albumin and LDH was seen in chicks fed T-2 toxin singly or in combination with DON. In neither case was additivity observed. Singly T-2 toxin and DON exposure resulted in a slight but statistically insignificant decrease in serum cholesterol. In combination the toxins further and significantly, reduced serum cholesterol. However, the relevance of this is uncertain.

In two studies the interaction of T-2 toxin and DAS was investigated in broiler chickens (Hoerr *et al.*, 1980) and in laying hens (Diaz *et al.*, 1994). In the first study LD50 was determined for a single and multiple oral doses of the two toxins alone and in combination. Additive effects on lethality were seen for the combined exposure. In the second study, laying hens were fed for 24 days diets with no toxin or added, added pure T-2 toxin (2 mg/kg feed), pure DAS (2 mg/kg feed) or the combination of the two. The basal diet was analysed for the presence of various toxins and the only one detected was small amounts of DON (0.3 mg /kg). Singly both toxins induced oral lesions and significantly but transiently reduced egg production and feed intake. The effects of combined exposure of T-2 toxin and DAS were additive for reduced feed consumption and incidence of oral lesions. The effect on egg production varied considerably over the experimental period. Combined exposure caused a decline of egg production over the whole period. No significant changes were seen in body weights and only mild changes in plasma enzymes were observed.

Summary and conclusions

Although T-2 toxin, HT-2 toxin, deoxynivalenol and nivalenol appear to cause similar effects at the biochemical and cellular level and there are similarities in toxic effects, there are also substantial differences in the spectrum of toxic effects *in vivo*. Large, non-systematic potency differences between these toxins were seen when different endpoints are considered. Furthermore, there are very few studies addressing the combined effects of these toxins. Moreover, in most of these studies naturally contaminated feed was used which makes the attribution of a potential effect to a single toxin very difficult.

Inhibition of protein synthesis by binding to ribosomes is common to the toxins. When tested in cells *in vitro*, dose additivity was observed for T-2 toxin and some other trichothecenes, whereas antagonism was observed between T-2 toxin and DON. In the protein inhibition assay DON was hundred fold less potent than T-2 toxin and when tested at equimolar concentrations a competition for binding sites resulting in antagonism could be hypothesised. The antagonism between T-2 toxin and DON observed in the lymphocyte proliferation assay and in the yeast assay could be explained by a similar mechanism, but in neither case has this been proven.

In the *in vivo* study on pigs DON alone caused a reduced body weight gain. Combined with T-2 toxin antagonism was observed at the mid T-2 toxin dose. In the chicken study it appeared that DON and T-2 toxin had an additive effect on body weight gain, but only one dose of each toxin was tested. In these *in vivo* studies no synergistic interactions were observed, although each compound was administered at toxic doses.

In summary, dose additivity, but also antagonism has been observed for T-2 toxin, DON and nivalenol *in vitro*. *In vivo* only antagonism was observed for T-2 toxin and DON and no dose

additivity was observed. Nivalenol in combination with other trichothecenes has not been examined *in vivo*. Although there could be indications for dose additivity in some of the *in vitro* studies, at present the database describing possible effects of combined exposure of trichothecenes is very weak and not sufficient for establishing either the nature of combined effects or the relative potencies of the trichothecenes.

Therefore, at present, the Committee considers that the available data, while limited, did not support the establishing of a group TDI for all the trichothecenes evaluated. It is noted that synergism, which would certainly call for additional caution, has not been observed.

In its evaluation of the individual trichothecenes, the Committee assigned temporary TDIs to DON, nivalenol, T-2 toxin and HT-2 toxin pending, among other things, a group evaluation. The TDIs for nivalenol and T-2 toxin were also made temporary because of gaps in the database. Therefore, the Committee now established a full TDI for DON only and confirmed the t-TDI for nivalenol and the combined t-TDI for T-2 toxin and HT-2 toxin:

DON: TDI = 1 µg/kg bw/day
Nivalenol: t-TDI = 0.7 µg/kg bw/day
T-2 toxin and HT-2 toxin: combined t-TDI = 0.06 µg/kg bw/day

Recommendation

The Committee recommends that further studies should fill data gaps for the single toxins as identified in the previous evaluations.

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