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SCIENTIFIC COMMITTEE ON FOOD

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OPINION
OF THE
SCIENTIFIC COMMITTEE ON FOOD
ON
FUSARIUM TOXINS
PART 4[1]: NIVALENOL

(expressed on 19 October 2000)

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[1] The present opinion deals only with nivalenol and therefore does not address all the terms of reference outlined below for fusarium toxins in general. The Committee will address the general aspects when all the relevant individual toxins have been considered.

Opinion of the Scientific Committee on Food on Fusarium Toxins Part 4[1]: NIVALENOL
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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. 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.

Introduction

In the evaluation of Fusarium toxins the criteria for toxin selection have been:

- the toxins most commonly found in analytical surveys of cereals;
- the toxins for which there is a minimum of toxicological data.

The first group of toxins to be evaluated contains deoxynivalenol (SCF 1999), T-2 toxin, HT-2 toxin, nivalenol, fumonisin B1 (SCF 2000b) and zearalenone (SCF 2000a).

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The present evaluation deals with nivalenol; it is primarily based on the report prepared for the Nordic Council of Ministers "Fusarium toxins in cereals – a risk assessment" (Eriksen and Alexander, 1998).

Nivalenol

Description
Nivalenol is a mycotoxin produced by fungi of the Fusarium genus, *i.e. Fusarium cerealis (F. crookwellence) and Fusarium poae* and to a lesser extent also *Fusarium culmorum* and *Fusarium graminearum,* (nivalenol was first isolated from *F. nivale* Fn2B, an atypical strain of *F.sporotrichioides*). These fungi are abundant in various cereal crops (wheat, maize, barley, oats, and rye) and processed grains (malt, beer and bread). The fungi producing trichothecenes are soil fungi and are important plant pathogens that grow on the crop in the field. Chemically nivalenol belongs to trichothecenes, type B. (cited in Eriksen and Alexander, 1998; IARC, 1993).

Chemistry
Nivalenol: trichotec-9-en-8-one,12,13-epoxy-3,4,7,15-tetrahydroxy-,(3-alpha,4-beta,7-alpha)- $C_{15}H_{20}O_7$, MW: 312.35, CAS-No: 23282-20-4.

Synonyms: 12,13-Epoxy-3,4,7,15-tetrahydroxytrichothec-9-en-8-one, 3-alpha,4-beta,7-alpha,15-Tetrahydroxy-12,13-epoxytrichothec-9-en-8-one, 3-alpha,4-beta,7-alpha,15-Tetrahydroxyscirp-9-en-8-one.

The trichothecenes are in general very stable compounds, both during storage/milling and the processing/cooking of food, and they do not degrade at high temperatures (Eriksen and Alexander, 1998).

Biochemical aspects– and cellular changes and potential mode of action

Few studies have been performed to elaborate the mechanisms of the toxicity of nivalenol. Nivalenol was shown to inhibit protein synthesis in rabbit reticulocytes *in vitro,* with an ID_{50} of 2.5 µg/ml, probably by impairment of the ribosomal function. Polyribosomal breakdown was found in bone-marrow cells of mice exposed to 3.5 mg nivalenol/kg bw (Ryu et al., 1987). Nivalenol inhibited the synthesis of nucleic acids *in vitro* (Ueno and Fukushima, 1968). This response appeared at doses much higher than the inhibition of protein synthesis. The mechanism of nucleic acid inhibition is not known. Nivalenol (0.01 µg/ml) induces apoptosis in HL60 cells (Ueno et al., 1995).

Toxicokinetics

In swine given nivalenol in the diet in a dose of 0.05 mg nivalenol/kg bw twice daily, nivalenol was detected in the blood 20 min after ingestion. During the first 7.5 hours, 11-48 % was absorbed from the intestine and the blood plasma peak concentration was low (3-6 µg/l), mostly occurring 2.5-4.5 hours after feeding. When nivalenol was fed 16 hours prior to blood sampling, it was found that nivalenol was still absorbed from the intestine. Nivalenol was mainly excreted in the faeces (Hedman et al., 1997).

Metabolism

In swine given 0.05 mg nivalenol/kg bw in the feed twice daily for one or three days no metabolites were detected in plasma, urine or faeces (Hedman, 1996; Hedman et al., 1997).

The gastrointestinal microflora of unexposed swine did not form de-epoxidated metabolites of nivalenol. After one week of exposure to 2.5 or 5.0 mg nivalenol /kg in the feed microbiological adaptation apparently occurred as the microflora became capable of nivalenol de-epoxidation. It was also able to produce de-epoxidated metabolites of DON *in vitro* (Hedman and Pettersson, 1997). Such adaptation might explain decreased toxicity during more than one week of nivalenol exposure (Williams and Blaney, 1994).

In male rats given 5 mg nivalenol/kg bw orally 12 times with 2-3 days intervals, 80% of the orally ingested nivalenol was excreted in the faeces and 1 % in the urine as de-epoxy-nivalenol. Seven per cent of the ingested nivalenol was detected unmetabolised in the faeces and 1 % in the urine (Onji et al., 1989).

Toxicity

Acute/subacute toxicity

An oral LD50 of nivalenol (99 percent pure) of 38.9 mg/kg bw has been found in mice (C57BL/6CrSlc SPF mice). Intraperitonal, subcutaneous and intravenous routes of exposure gave LD50 values of 5-10 mg/kg bw. Most deaths occurred within 3 days after oral exposure and marked congestion and haemorrhage in the intestine were seen. Acute toxicity in mice also includes lymphoid organs (Ryu et al., 1988). In Fischer 344 rats the oral and subcutaneous LD50 nivalenol were 19.5 and 0.9 mg/kg bw, respectively giving sedation, diarrhoea and congestion of the lungs and digestive tract (Kawasaki et al., 1990, cited in IARC, 1993).

Female mice given 30 mg nivalenol /kg diet (about 3.5 mg/kg bw) for 24 days had significant erythropenia and slight leukopenia. No changes were seen in other haematological parameters, feed consumption, body weight gain or organ weights of liver, spleen or thymus. Ultra-structural studies demonstrated polyribosomal breakdown of the bone-marrow cells. Mice given 10 mg/kg diet had no changes (Ryu et al., 1987).

In rats given 0.4 and 2.0 mg/kg bw daily for 30 days no significant changes were detected in biological and haematological parameters. The weight of the liver and spleen were slightly increased, but no histological change was seen (Kawasaki et al., 1990, cited in IARC, 1993).

Rats given nivalenol from pulverised mould as described by Ryu et al. (1988) in doses of 0, 6 and 12 mg/kg feed for 4 weeks showed decreased feed uptake, terminal weight gain, and organ weights and changes in P-450 and glutathione transferase activity were observed (Yabe et al., 1993).

Subchronic toxicity

Mice (C57BL/6CrSlc SPF mice) were fed pulverised *F. nivale* (claimed by the authors not to produce other trichothecenes on rice) grown on polished rice in doses 0, 6, 12 or 30 mg nivalenol /kg feed (0, 0.7, 1.4 or 3.5 mg nivalenol /kg bw) for 4 or 12 weeks. Reduced body weight gain and feed consumption was observed. A statistical decrease in relative organ weight was observed in thymus and spleen in females on the highest dose after 4 weeks and in spleen

and kidneys in males on the two highest doses. After 12 weeks, a reduction in relative organ weight was only found in liver of both males and females. No histopathological changes were observed in thymus, spleen, brain, pituitary gland, stomach, kidneys, adrenal glands, liver, small intestine with or without Peyers patch, mesenterial lymph node, ovaries, sternum or femurs (Yamamura et al., 1989).

Chronic toxicity and carcinogenicity

Female mice (C57BL/6CrSlc SPF mice) were given feed containing pulverised *F. nivale* (claimed by the authors not to produce other trichothecenes on rice with no detectable fusarenon-X (4-acetyl nivalenol)). The doses were 0, 6, 12 or 30 mg/kg feed (0, 0.7, 1.4 or 3.5 mg nivalenol /kg bw) for one or two years. Decreased body weight gain and feed consumption were seen in all treated groups. The absolute weight of the liver was significantly reduced in the group receiving 3.5 mg/kg bw and the kidney weight in the groups receiving 1.4 and 3.5 mg nivalenol/kg bw. Severe leukopenia was also observed in the treated animals treated for one year also at the lower dose, whereas the white blood cell count was not affected in the two year study. No histopathological changes including tumours were found in liver, thymus, spleen, kidneys, stomach, adrenal glands, pituitary glands, ovaries, bone marrow, lymph node, brain and small intestines with or without Peyers patch (Ryu et al., 1988, Ohtsubo et al., 1989). A lowest observable adverse effect level (LOAEL) derived from these studies was 0.7 mg/ kg bw with growth inhibition and leukopenia as effects. A no observable adverse effect level (NOAEL) could not be derived from these studies.

IARC (1993) concluded that there is inadequate evidence of carcinogenicity of nivalenol in experimental animals. No human data were available. The overall conclusion was that the carcinogenicity was not classifiable (group 3).

Genotoxicity

Nivalenol slightly increased the frequencies of chromosomal aberrations and sister chromatid exchange in Chinese hamster V79 cells (Hsia et al., 1988). Using single cell gel electrophoresis (Comet assay) Tsuda et al. (1998) investigated DNA damage/ DNA strand breaks in cultured CHO cells and several mouse organs. Nivalenol 50 and 100 µg/ml damaged DNA (DNA strand breaks). Mice were given 20 mg nivalenol /kg bw orally or 3.7 mg /kg bw ip. DNA damage (Comet assay) appeared in the kidney, bone marrow stomach, jejunum and colon but not in thymus or liver. Upon histopathological examination no necrotic changes were observed in the organs with DNA damage. The available data do not allow an adequate evaluation of the genotoxicity.

Developmental toxicity studies and studies on reproduction

ICR mice were injected i.p. 0, 0.1, 0.5 and 1.5 mg purified nivalenol/kg bw on days 7-15 of gestation (10 animals in each group). The highest dose caused stillbirth in 6 of 10 mice. 48 and 88 % embryolethality was observed in mice given 0.5 and 1.5 mg/kg bw respectively. No foetal malformation was observed. No effect was observed in mice receiving 0.1 mg/kg bw /day(Ito et al., 1986). In another study by the same group, ICR mice were given mouldy rice containing 6, 12 and 30 mg nivalenol/kg feed throughout the gestation. In addition, purified nivalenol was given to 4 groups of mice in doses from 1-20 mg nivalenol/kg bw by gavage on day 7-15 of gestation. Embryotoxicity was observed in the groups receiving 30 mg/kg in the diet and in

mice receiving 10 mg nivalenol/kg bw or more by gavage on day 7-15 of gestation. Maternal toxicity was observed at these doses. Intrauterine weight retardation was observed in foetuses from mice receiving 12 mg/kg feed (1.4 mg /kg bw), and 5 mg/kg bw by gavage on days 7-15 of gestation (Ito et al., 1988 (in Japanese), cit. WHO, 1990).

Nivalenol is embryotoxic in mice, but there is no evidence of teratogenicity. The LOAEL in reproduction studies with nivalenol given by oral exposure was stated to be 1.4 mg/kg bw given in the feed throughout gestation and 5 mg/kg bw when given by gavage on days 7-15 (Ito et al., 1988 (in Japanese), cit. WHO 1990). Data from other species are lacking.

There are no data on reproductive effects in adult males and females.

Immunotoxicity/haematotoxicity

Acute nivalenol induces bone marrow toxicity. Erythropenia and slight leukopenia were seen in mice given 3.5 mg/kg bw for 24 days. Acute toxicity also includes lymphoid organs (Ryu et al., 1988). Long-term exposure may also result in leukopenia. (This has been described in the section Acute/subacute toxicity.)

Nivalenol inhibits blastogenesis in cultured human lymphocytes. It produced a 50 % inhibition of the incorporation of thymidine in mitogen-stimulated human peripheral lymphocytes at a concentration of 72 ng/ml. (Forsell and Pestka, 1985). Thuvander et al. (1999) found that nivalenol inhibited proliferation of human male and female lymphocytes stimulated with phytoheamagglutin (PHA) (IC50: 350 nM) and pokeweed (PW) (IC50: 270 nM). Nivalenol also inhibited immunoglobulin production induced by PW. Effects were seen in the same concentration range as were seen for deoxynivalenol (DON). T-2 toxin was 100 fold more toxic. Combination of nivalenol with T-2 toxin, DAS or DON resulted in an additive effect.

Furthermore, in mice given 6 or 12 mg nivalenol/kg feed an increase in serum IgA was observed accompanied by immunopathological changes in kidneys analogous to human IgA-nephropathy was observed (Hinoshita et al., 1997).

Nivalenol inhibited total and antigen specific IgE production in ovalbumin specific T cell receptor αβ transgenic mice (Choi et al, 2000). Interleukin 4 was suppressed while interleukin 2 was increased.

Effects on nervous system

No data were available.

Effects in humans

No data were available.

Evaluation and Conclusion

The general toxicity and immunotoxicity/haematotoxicity of nivalenol are considered the critical effects. From long term studies in mice, these effects are similar to those of other trichothecenes.

It should be noted that signs of forestomach papillomas or - hyperplasia or other tumourigenic effects (as were reported for T-2 toxin) were not detected in the long term mice studies.

There is only limited information on the genotoxicity of nivalenol.

The evaluation is based on a threshold approach and the following LOAELs are considered.
Oral LOAELs of nivalenol

Study	Critical Effect	LOAEL/NOAEL (mg/kg bw/day)	Reference
Mouse, 2 years (in feed)	Growth retardation, leukopenia	0.7 (LOAEL)	Ohtsubo et al., 1989
Mouse, 1 year (in feed)	Growth retardation, leukopenia	0.7 (LOAEL)	Ryu et al., 1988
Mouse, throughout gestation period (in feed)	Intrauterine growth retardation	1.4 (LOAEL)	Ito et al., 1988 (in Japanese), cit. WHO, 1990
Mouse, 7-15 day of gestation (by gavage)	Intrauterine growth retardation	5 (LOAEL)	Ito et al., 1988 (in Japanese), cit. WHO, 1990

Only LOAELs are available from the oral route in the long-term studies and reproductive studies. For a risk assessment the oral route is regarded as most relevant.

It was noted that nivalenol used in the long-term studies were produced by *F. nivale* and claimed by the authors not to produce other trichothecenes.

It was decided to use the LOAEL (0.7 mg/kg bw) from the long-term dietary studies with mice. A large uncertainty factor of 1000 was applied because of the use of a LOAEL and a limited database. A temporary TDI (t-TDI) of 0-0.7 µg/ kg bw/day was derived.

The TDI is made temporary because it is noted that nivalenol belongs to the group of several trichothecenes with a common basic chemical structure, which are produced by *Fusarium* fungi (e.g. DON, T-2- and HT-2 toxin), and according to present knowledge they may also share common mechanisms of toxic action. Once the other most important trichothecenes have been evaluated, the Committee will consider the combined total exposure to trichothecenes and whether a group TDI should be assigned.

<u>Risk characterisation</u>

The mean daily intake of nivalenol from cereals has been estimated in the Nordic countries (Eriksen and Alexander, 1998) and was found to be 0.05-0.09 µg/kg bw., which is one order of magnitude below the t-TDI. It should be noted that the trichothecene fusarenon X (4-acetyl-nivalenol), which is rapid deacetylated to nivalenol in vivo often occurs together with nivalenol in amounts 10-20 % that of nivalenol (Eriksen and Alexander, 1998). Animal products do not appear to be a significant source of nivalenol (Jonker et al., 1999).

<u>Needs for future studies</u>

There is a need for a long-term study with doses making it possible to derive a NOAEL.
The immunotoxicity/haematotoxicity should be studied using long-term exposure to low doses and assessing the function of the immune system e.g. resistance to infection etc.
There are no studies on the neurotoxicity of nivalenol. Several trichothecenes have shown neurotoxic effects. Studies are needed to cover the trichothecene group as a whole including nivalenol, to confirm that there are no neurotoxic effects at doses below those causing effects on growth and body weight, focussing on the known target for trichothecenes, the CNS serotonergic system.
Comparative toxicity and toxicokinetic studies in rodents and pigs might allow insight in species differences.
Further genotoxicity studies are also recommended on gene and chromosome level.
There is a need for more accurate information on the exposure to nivalenol (and other trichothecenes) in Europe.

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