Available online at www.sciencedirect.com
SCIENCE DIRECT®
Toxicology Letters 153 (2004) 155–163
Toxicology Letters
www.elsevier.com/locate/toxlet

The risk assessment paradigm and its application for trichothecenes

Angelika M. Tritscher, Samuel W. Page*

International Programme on Chemical Safety, World Health Organization, Avenue Appia, 20, CH 121, Geneva 27, Switzerland

Available online 28 July 2004

Abstract

Risk analysis for trichothecene mycotoxins and other food contaminants, which are to a significant extent unavoidable, presents considerable challenges. Risk assessment is constrained by uncertainties associated with the lack of adequate data, and risk management must consider the fact that mycotoxin contamination can have serious impacts on trade and food sufficiency. These factors necessitate good communication between the risk assessors and risk managers in formulating the questions to be addressed by the risk assessment. Risk assessment must be an iterative process, since the problem formulation and the risk assessment may need to be revised to reflect new data and theories. In addition to providing advice to risk managers, risk assessment should provide a blueprint for future research by illustrating what observations will influence a prediction. The international risk assessments completed for deoxynivalenol, T-2 and HT-2 toxins, and nivalenol have noted a number of issues regarding the lack of adequate intake data for exposure assessment and significant gaps in toxicological studies for hazard characterizations. Addressing these uncertainties would provide risk managers with better guidance for control measures.

Keywords: Trichothecenes; Mycotoxin; Risk assessment; Deoxynivalenol; T-2 and HT-2 toxins; Nivalenol

1. Introduction

The risk assessment paradigm as generally practiced was elaborated by the U.S. National Research Council in 1983 (National Research Council, 1983). This has been incorporated in most risk analysis frameworks, such as that of the Codex Alimentarius Commission (Codex Alimentarius Commission, 2003). The functioning of the risk analysis process continues to evolve and be debated, particularly the separation between the roles of the risk assessors and the risk managers. This separation or lack thereof can be particularly problematic when risk management considerations are thrust upon risk assessors. Risk assessments must be objective scientific judgements.

Risk analysis for trichothecenes and other food contaminants, that are to a significant extent unavoidable, presents considerable challenges. Risk assessment is constrained by uncertainties associated with the lack of adequate data, and risk management must consider, in addition to the health consequences, the fact that mycotoxin contamination can have serious impacts on trade and food sufficiency. These factors necessitate good communication between the risk assessors and risk managers in formulating the questions to be addressed by the risk assessment. This is especially critical for the risk assessment of unavoidable

* Corresponding author.
E-mail address: pages@who.int (S.W. Page).

0378-4274/$ – see front matter
doi:10.1016/j.toxlet.2004.04.030

contaminants. Risk assessment must be an iterative process, since the problem formulation and the risk assessment may need to be revised to reflect new data and theories (see Renwick, 2003).

Risk assessment involves the following four components:

1. Hazard identification—identifies via in vitro and in vivo methods the potential target(s) and the potential endpoint(s) of toxicity.
2. Hazard characterization—includes dose-response considerations and evaluation of the relevance of certain endpoints in experimental systems for humans (from such data in the pivotal study, no observed adverse effect levels (NOAEL/NOEL), or lowest observed adverse effect levels (LOAEL/LOEL) can be identified).
3. Exposure assessment—integrates occurrence and food consumption data.
4. Risk characterization—integrates information from hazard characterization and exposure assessment into advice suitable for risk management decisions. This advice can be a quantitative estimate of health risk at certain exposure levels, or it can be in form of a level of exposure without significant adverse health effects, such as the acceptable daily intake (ADI) or the tolerable daily intake (TDI) (including provisional (P) and temporary (t) qualifying designations). ADIs are generally designated for substances intentionally added or present as a result of other approved intentional uses, such as pesticide residues. TDIs are used for unavoidable contaminants. Comparison of these values with the estimated exposure helps in the identification of critical foods or critical target populations in case the ADI/TDI is approached or even exceeded, and can so help in directing risk management measures.

Of the more than 180 known trichothecene mycotoxins, deoxynivalenol (DON), nivalenol (NIV), and T-2 toxin (T-2) are considered to be the most important with respect to their presence in feeds and foods. Their chemical structures were determined over 30 years ago. Prior to that time, there had been numerous animal and some human toxicoses associated with grains contaminated with various species of *Fusarium*. Since that time, there have been additional outbreaks and numerous in vitro and in vivo laboratory studies. There is widespread human exposure to several of these mycotoxins. In animal studies, there is evidence of potent immunomudulation. However, other than some evidence for acute gastrointestinal effects at relatively high doses associated with DON and suspected involvement of T-2 toxin in historical outbreaks under unusual circumstances, adverse effects have yet to be demonstrated in humans. Since human exposure is to mixtures of the trichothecenes and often other mycotoxins as well, the combined toxic effects may be relevant, but are difficult to assess (see Speijers and Speijers, 2004).

Several national health organizations, the Nordic Council of Ministers (Eriksen and Alexander, 1998), the joint FAO/WHO Expert Committee on Food Additives (JECFA) (Canady et al., 2001, 2001a) and the European Commission Scientific Committee on Food (SCF) (Scientific Committee on Food, 1999, 2000, 2001, 2002) have carried out risk assessments for the most common trichothecene mycotoxins. In this review, the results of the JECFA and SCF reviews will be highlighted.

In addition to providing advice to risk managers, risk assessment should provide a blueprint for future research by illustrating what observations will influence a prediction. Since most of the considerations for the risk assessment steps for the trichothecenes are discussed elsewhere (Schlatter, 2004; Schothorst and van Egmond, 2004; Pieters and Bakker, 2004), this paper will focus on the additional research that is needed to reduce the uncertainties in these risk assessments.

1.1. Hazard identification and characterization

Hazards associated with most mycotoxins, including the trichothecenes, were first recognized from livestock toxicoses caused by mycotoxin-contaminated feed. As studies in experimental animals and in vitro were carried out, other adverse effects were identified. The pivotal adverse effects that have been used for the risk assessments of the trichothecenes include immunotoxicity, haematotoxicity, and reduction in body weight gain. At low levels of exposure, most of these effects appear to be reversible. However, questions remain about these and other toxicological end points of concern. In vitro and in vivo studies have shown that lower doses of the trichothecenes can result in immune stimulation, whereas high doses can result in immune suppression. The potential role of the trichothecenes

in human immune dysfunction and haematotoxicity, including increased susceptibly to infectious diseases and adverse effects on the outcome of immunisations, remains to be determined (see Meky et al., 2001).

While there is no convincing evidence that any of the trichothecenes are genotoxic or carcinogenic, additional studies have been recommended. In view of the widespread human exposure to DON, JECFA recommended that further studies of the genotoxicity of DON be conducted, as well as a study of the carcinogenicity in a second species (rat) (Canady et al., 2001). JECFA also recommended further studies to reduce the uncertainty in the evaluation of the carcinogenic potential of T-2 toxin and that standard bioassays in rats and mice, with pair-fed controls, would be preferred (Canady et al., 2001a). For NIV, the SCF recommended further genotoxicity studies and a long-term study with doses for the derivation of a NOAEL (Scientific Committee on Food, 2000).

JECFA (Canady et al., 2001a) and the SCF (Scientific Committee on Food, 2001) recommended the immunotoxicity/haematotoxicity of T-2/HT-2 should be investigated by the use of sensitive end-points with response to low dose–effects and time course in longer-term exposure studies where feed intake is controlled. Also, JECFA concluded that a longer-term study in pigs is needed in which a NOEL is identified, control groups are used to account for the potential effects of reduced feed consumption, and relevant, sensitive end-points of haematotoxicity and immunotoxicity are measured.

Since there are considerable species differences in sensitivity for the trichothenes, both SCF and JECFA suggested that additional comparative studies of toxicity and toxicokinetics should be carried out in several species, such as rodents, cats, and pigs. The SCF noted that studies of metabolism of T-2 toxin in human in vitro models would also be helpful.

The SCF (Scientific Committee on Food, 2000) recognized the need for a long-term study of NIV with doses making it possible to derive a NOAEL.

Since several trichothecenes have shown neurotoxic effects, the SCF (Scientific Committee on Food, 2001) recommended additional studies to confirm that there are no neurotoxic effects at doses below those causing effects on growth and body weight, focusing on the known target for trichothecenes, the CNS serotonergic system.

The reports associating trichothecene contamination with adverse effects in human populations have not been definitive. However, the weight of evidence of these studies clearly implicates these mycotoxins in human and animal toxicoses. As has been noted, human exposure in mycotoxin-contaminated food is usually to a mixture of mycotoxins. JECFA and the SCF noted that studies are needed of the combined effects of the trichothecenes that contaminate foods consumed by humans. In none of the outbreaks reported, has there been a precise association of the analytical results of specific samples with specific cases of illness or lack of illness. JECFA (Canady et al., 2001a) recommended that more detailed, analytical epidemiological studies should be conducted in those areas of the world where the presence of scabby wheat or mouldy maize is a cyclic, endemic event. Such data would help to establish a dose response relationship between the intake of DON (and other trichothecenes) and acute illness, and allow the identification of a NOAEL based on human data. The recent development of DON-glucuronide as a urinary biomarker of human exposure to DON should facilitate epidemiological studies of disease associations with DON. (Meky et al., 2003). Concurrent with the very rapid evolution and application of techniques to measure biomarkers of effect, such as immune responses, the critical tools for the molecular epidemiology that can better address risk assessment questions would appear to be in place. However, given the high sensitivity of some of these measurement techniques, the determination of the “adverse” in NOAEL will become more important.

1.2. Exposure assessment

In the context of the tiered risk assessment process, the efforts put into exposure assessment should be influenced by the risk identification and characterization. The quantitative evaluation of the likely intake of mycotoxins on an international basis is extremely problematic. With the expansion of the EU, this will also become more of an issue there. Food consumption patterns and production and processing practices vary considerably, and these data are often not available from many countries. In addition, data for exposure assessment for subpopulations such as children, pregnant women or the elderly are usually not available.

Historically, JECFA has had available mainly pooled data for mycotoxin contamination, so intake estimation was based on a combination of mean food consumption levels with weighted-mean contamination levels of the five GEMS/FOOD regional diets (African, European, Far Eastern, Latin American, and Middle Eastern) (WHO, 1998). While most mycotoxin risk assessments by JECFA have been for chronic exposure, for some of the trichothecenes, particularly DON, acute exposure data is also important due to concerns for acute toxicity. JECFA and the SCF recognized the need for more adequate information on the exposure to the trichothecenes. The EC SCOOP Task 3.2.10 "Collection of occurrence data of *Fusarium* toxins in food and the assessment of dietary intake by the population of EU member states" will provide additional data for the assessment of dietary intake in the EU (Schothorst and van Egmond, 2004). As a result of the complexity of assessing exposures and providing better guidance to risk managers, probabilistic approaches may need to be applied. These will require more complete data sets and not just the pooled or mean data that has been usually submitted for the GEMS/Food database.

1.2.1. DON

For the intake assessment for DON, JECFA used a total of 375 data points representing about 23,000 individual samples (Canady et al., 2001). Of these data points, 243 were reported from countries with the European-type diet. Data on processed food products were excluded, since the GEMS/Food regional diets are based on the data for raw or minimally processed foods only. The results of the intake assessments are given in Table 1. JECFA recommended that for surveys of concentrations of DON, the accuracy and comparability of analytical measurements of the toxin in processed foods should be improved. Additional data on the distribution of contamination and national food consumption patterns, particularly in countries where DON is prevalent, are needed. Information on the effects of processing and its impact on levels of contamination by DON are needed for better estimates of dietary intake.

Table 1
JECFA intake assessments for DON

Region	Total intake (μg/kg bw per day)
African	0.78
European	1.4
Far eastern	1.6
Latin American	1.2
Middle eastern	2.4

1.2.2. T-2/HT-2 Toxins

As little information on the concentrations of T-2 and HT-2 toxins in food commodities was available from geographical regions other than Europe, JECFA's dietary intake estimate was only on the basis of the GEMS/Food European regional diet. The average intake of T-2 toxin was estimated to be 8 ng/kg bw/day, and that of HT-2 toxin was estimated to be 9 ng/kg bw/day. The Nordic Council of Ministers average daily intake estimates for T-2 and HT-2 from cereals was 130 ng/kg bw (Eriksen and Alexander, 1998).

1.2.3. NIV

The mean daily intake of NIV from cereals has been estimated to be 0.05–0.09 μg/kg bw in the Nordic countries (Eriksen and Alexander, 1998). The SCF noted that there is a need for more accurate information on the exposure to NIV and other trichothecenes in Europe.

1.3. Risk characterization

In animal models, the trichothecene mycotoxins can affect the immune and haematological systems, and cause growth retardation and adverse reproductive effects. A common mechanism of action via inhibition of protein synthesis and induction of apoptosis may be hypothesised, but this has not been shown for all these toxins.

Since there is no convincing evidence that any of the trichothecenes are genotoxic, a threshold for toxicity is generally accepted. A NOAEL or LOAEL can be determined. Based on the type of critical effect and the overall quality of the data, a safety factor that takes into account species differences and variations in humans is selected to establish the threshold for the adverse effect in humans.

1.3.1. DON

On the basis of decreases in body weight as the adverse effect in a 2-year feeding study in mice,

JECFA (Canady et al., 2001) and the SCF (Scientific Committee on Food, 1999) established a provisional maximum tolerable daily intake (PMTDI)/temporary tolerable daily intake (tTDI) of 1 μg/kg bw on the basis of the NOAEL of 100 μg/kg bw/day and a safety factor of 100. They concluded that intake at or below this level would not result in effects of DON on the immune system, growth, or reproduction or result in acute gastrointestinal effects. However, comparing this PMTDI with estimated exposure indicates that for DON, the PMTDI may be exceeded in certain regions of the world or for certain parts of the population. A probabilistic exposure assessment for DON in The Netherlands has been carried out using daily intakes of DON in 6247 individuals for two consecutive days (Pieters et al., 2001). This study indicated that during the time period under consideration, young children had the highest relative exposure to DON, often at levels exceeding the PMTDI.

1.3.2. T-2/HT-2 Toxins

JECFA (Canady et al., 2001a) and the SCF (Scientific Committee on Food, 2001) used the LOEL of 0.029 mg/kg bw/day for haematological changes in a 3-week dietary study in pigs. Since there was no clear NOEL and no study of long-term administration, as well as considerable sex, species, and individual variations in sensitivity, a safety factor of 500 was used to derive a provisional maximum tolerable daily intake (SCF:temporary TDI) for T-2/HT-2 of 0–60 ng/kg bw/day.

JECFA noted that exposure would not be expected to exceed the group PMTDI of 60 ng/kg bw/day, but that more accurate information on human intake in various regions of the world and improved analytical methods are needed. However, recent studies indicate that, depending on how contamination lower than the limits of detection of the analytical methods are calculated, the PMTDI could be exceeded (Schothorst and van Egmond, 2004). JECFA noted that dietary intake data for T-2/HT-2 toxins in geographical regions in addition to Europe, should be evaluated when more data on the concentrations become available. The SCF recognized the need for more adequate information on the exposure to T-2/HT-2 and other trichothecenes, i.e., occurrence in food commodities and intakes.

1.3.3. NIV

The SCF (Scientific Committee on Food, 2000) determined a temporary TDI of 0–0.7 μg/kg bw/day for NIV from the LOAEL (0.7 mg/kg bw/day) from the long-term studies in mice. An uncertainty factor of 1000 was applied because of the use of a LOAEL and the limited database. There are only limited data on intake; however, the estimate from the Nordic countries indicates that intake may be well below the t-TDI.

1.4. Unresolved issues

1.4.1. Group TDIs/toxic equivalency factors

In general, the establishment of a group TDI for several compounds should be considered when they share a common mechanism of action/common active metabolite and there is frequent co-exposure. The addition of the doses from several compounds at the molecular target could result in an effect even if the dose of each single compound is below the threshold dose for effect. The development of a group TDI requires the knowledge of the potency of the single compounds in question. When the relative toxicities have been determined, toxic equivalency factors (TEFs) can be developed for the determination of the group TDI. In the case of synergistic or antagonistic effects resulting in a deviation from additivity, the establishment of a group TDI may be problematic in cases where the combined effects depend on the dose and only toxicity studies of the individual compounds are available. This is particularly true for data generated by using overtly toxic doses.

JECFA and the SCF determined that a group TDI for T-2 and HT-2 toxin was justified. They very frequently co-occur. Their toxic potencies are in the same range. T-2 is rapidly metabolised to HT-2, and, therefore, their toxic effects could not be differentiated.

The SCF (Scientific Committee on Food, 2002) determined that the available data does not support the establishing of a group TDI for DON, NIV, T-2, and HT-2 toxin. While these mycotoxins appear to cause similar effects at the biochemical and cellular level, as well as in vivo, there are also substantial differences in the spectrum of toxic effects and large, non-systematic potency differences among species. JECFA recommended that toxic equivalency factors be developed for the trichothecenes if sufficient data become available (Canady et al., 2001). Since DON

is the most extensively studied trichothecene, JECFA further recommended that toxic equivalence factors be established relative to DON.

The SCF recommended that the role of 3-acetyl-DON, which is prevalent in Europe, and 15-acetyl-DON, which is relevant in North America, should be investigated (Scientific Committee on Food, 1999). These toxins are often present at levels of 10%–20% DON, and differ only with an acetyl group. Research should be carried out to investigate the rate and degree these toxins are metabolised to DON to clarify if they can be assessed together with DON.

Fusarenone-X is rapidly deacetylated to NIV in vivo and often co-occurs with NIV in amounts 10%–20% of NIV. Therefore, a group TDI should be considered for these two compounds (Scientific Committee on Food, 2000).

Many other trichothecenes have been identified as contaminants, but the available data indicate there is only limited human exposure. Therefore, efforts to develop information to include them in a group TDI would not be a high priority.

1.4.2. Exposure above the TDI

The significance of excursions of intake above the TDI has been discussed in detail at a previous ILSI Europe workshop (Larsen and Richold, 1999). The following are among the points raised at this workshop.

- The likelihood of any health risk from intakes above the TDI depends on the duration and magnitude of excess intake in relation to the toxicological database, and the pivotal study used to derive the TDI.
- The severity of the effect in sensitive and high-intake individuals depends on the magnitude of the excess intake, the nature of the critical effect, and the slope of the dose–response curve.
- An increased risk of an adverse effect following intakes above the TDI would occur only if they were of sufficient duration to produce an intake-related and proportional increase in intracellular concentrations of the active chemical and to produce the cellular changes which result in the toxic response.
- Since the TDI is usually based on a chronic study, an intake above the TDI should not be acceptable if it occurred throughout the major part of human life because it reduces the overall safety margin.
- When excess intake is for a period shorter than the pivotal study on which the TDI was based, consideration should be given to using a NOAEL from a study of shorted duration to determine whether the excess intake is indeed of concern. This is because use of the NOAEL from the pivotal study (usually chronic) might under these specific conditions be too conservative and overestimate the actual risk.
- Important considerations are the degree of reversibility, toxicokinetics, and toxicodynamics.
- Excursions of intake above the TDI theoretically moves the most sensitive individual from negligible risk to possible risk.

JECFA recognized that, based on the single weighted mean concentrations and the GEMS/Food regional diet, the PMTDI for DON would be exceeded for four of the five regional diets. Studies in The Netherlands indicated that this was the case for people younger than 20 years during the period September 1998–January 2000 (Pieters et al., 2001). Assuming a concentration of one-half of the limit of detection for all samples below the limit of detection, data collected during the SCOOP project indicate that for both DON and T-2 toxin, there is considerable exposure above the TDIs for these mycotoxins (Schothorst and van Egmond, 2004).

The risk assessment of DON by RIVM considered children (1–4 years) the population at risk in The Netherlands, with growth retardation as the critical toxic effect (Pieters et al., 2001). Table 2 shows estimated intakes of DON by young children taken from the RIVM and JECFA reports.

Table 2
Estimated intake of DON by young children (μg/person/day)

Argentina	35[a]
The Netherlands	8.3[b], 11.7[c]
UK	49[d]
USA	51[e]

[a] Children 1–5 years, eaters only, weighted mean (Canady et al., 2001).
[b] Females, 1–4 years, eaters only, mean (Pieters et al., 2001a).
[c] Males, 1–4 years, eaters only, mean (Pieters et al., 2001a).
[d] Children 1.5–4.5 years, eaters only, 97.5th percentile (Canady et al., 2001).
[e] Children 1–6 years, 3-day average, 97.5th percentile (Canady et al., 2001).

Table 3
Range of concentrations of DON in GEMS/food regional diets (μg/gm) (Canady et al., 2001)

Region	Maize	Wheat
African	ND – 2,800	NA
European	ND – 19,000	ND – 21,000
Far eastern	ND – 6,500	ND – 20,000
Latin American	ND – 4,300	ND – 30,000

1.4.3. Acute reference dose (acute RfD)/Acute TDI

The acute RfD of a chemical is an estimate of a substance in food and/or drinking water, expressed on body weight basis, that can be ingested as a short term intake recorded on a daily basis, usually as a single day's consumption, without appreciable health risk to the consumer on the basis of all known facts at the time of evaluation. An acute RfD/TDI is particularly relevant when there is a likelihood of spikes in the occurrence/intake of the substance. Acute RfDs are commonly used for plant protection products if there are indications that acute toxicity is relevant. The joint FAO/WHO meeting on pesticide residues developed guidance for evaluations for acute RfD (FAO/WHO, 2002).

The period over which intake is estimated corresponds to the toxicological end point of concern. For acute intakes, comparison to a TDI based on chronic data may greatly overestimate the risk. JECFA noted that from the animal studies, DON may have adverse health effects after single, short term, or long term administration (Canady et al., 2001) The acute symptoms of DON poisoning in animals include feed refusal, diarrhoea, and vomiting. At high doses, gastrointestinal damage was observed. DON was teratogenic at high doses in several animal studies. However, there are considerable differences in species sensitivities to the acute affects of DON. JECFA recognized that DON can cause outbreaks of acute illness in humans, but suggested the available data did not permit the establishment of a level below which no acute effects would be expected to occur. In the opinion of the SCF, the tTDI of 1 μg/kg bw/day would also protect against the acute effects of DON (Scientific Committee on Food, 1999).

The range of concentrations of DON in grains for the JECFA review is given in Table 3. During periods with adverse weather conditions, the incidence of high levels of contamination can be very problematic. From the available data, the occurrence of DON and T-2/HT-2 is highly variable and "spikes" are highly possible.

2. Conclusions

DON is a frequent contaminant of dietary staples, particularly wheat- and corn-based, in many areas of the world. From the limited data that is available, contamination of small grains in Europe with T-2 and HT-2 toxins is also common. Table 4 summarizes the recommendations for TDIs by several international expert committees.

Little additional information has been generated since these risk assessments that would result in a significant revision of the conclusions. These risk assessments include considerable uncertainties. There are inadequacies in intake data, information on toxicokinetics and mechanisms of actions, and comparative potency data. Some questions remain about the potential for carcinogenicity of the trichothecenes. Studies on their immunotoxicity have raised more questions than they have answered with regard to adverse effects in humans (see Pestka, 2004).

Improved intake information is a universal need for the risk assessment of the trichothecenes. Consensus regarding the calculations of occurrence below the limits of detection of the analytical methods

Table 4
Summary of multinational risk assessments for trichothecene mycotoxins

Compound	Critical effect (LOEL/NOEL (mg/kg bw/day))		Uncertainty/safety factor	TDI—PMTDI or tTDI (μg/kg bw/day)
	Growth Retardation	Immuno-toxicity		
DON	0.1 (NOAEL)		100	1
NIV	0.7 (LOAEL)	0.7 (LOAEL)	1000	0.7
T-2/HT-2		0.03(LOAEL)	500	0.06

should be developed. Probabilistic data analysis techniques can provide risk assessors and risk managers more meaningful information on exposure, particularly distributions and intake by population subgroups.

There are several hazard/risk characterization issues that are particularly conspicuous in the lack of adequate information for assessments.

- Since the trichothecenes are present as mixtures and common mechanisms of toxicity have been proposed, development of information for the establishment of group TDIs should be addressed.
- Excursions above the TDIs for DON and T-2/HT-2 toxins occur with some regularity in certain population subgroups. In the JECFA risk assessment, the mean intake exceeded the PMTDI in four of the five GEMS/Food regional diets. In Europe, while the mean dietary intakes of DON are usually less than the tTDI for the entire population and adults, they are close and even exceed the tTDI's for infants and children. In Europe, based on estimates of occurrence below the limits of detection, intakes of T-2/HT-2 can exceed the tTDI. The significance of (occasional) intake above the TDIs need to be addressed.
- According to the criteria for the acute RfD, the establishment of an acute TDI should be considered for DON and T-2/HT-2, possibly by applying the guidelines established for residues of pesticides in food (FAO/WHO, 2002).
- But the most significant lack of information is the effects on chronic, low dose exposure in humans. Priority should be given to epidemiological studies in populations where exposure to the trichothenes is chronic and higher. The validated human urinary biomarker of exposure for DON is an important tool for these studies. As advances in molecular epidemiology to identify biomarkers of effect are applied, suspected effects may be confirmed and unrecognized and confounding effects determined. However, a key consideration will be to distinguish the adverse effects from those that are not adverse.

Addressing these uncertainties would provide risk managers with better guidance for prioritization of control measures.

Acknowledgements

The ILSI Europe Natural Toxins Task Force supported the workshop at which this work was presented.

References

Canady, R.A., Coker, R.D., Egan, S.K., Krska, R., Kuiper-Goodman, T., Olsen, M., Pestka, J., Resnik, S., Schlatter, J., 2001. Deoxynivalenol. In WHO/IPCS Safety evaluation of certain mycotoxins in food. WHO Food Addit. Ser. 47, 419–555, http://www.inchem.org/documents/jecfa/jecmono/v47je05.htm.

Canady, R.A., Coker, R.D., Egan, S.K., Krska, R., Olsen, M., Resnik, S., Schlatter, J., 2001a. T-2 and HT-2 toxins. In WHO/IPCS Safety evaluation of certain mycotoxins in food. WHO Food Addit. Ser. 47, 557–680, http://www.inchem.org/documents/jecfa/jecmono/v47je06.htm.

Codex Alimentarius Commission, Report of the 26th Session of the Codex Alimentarius Commission, 2003, ALINORM 03/41, Appendix IV. http://www.fao.org/codex/alinorm03/a103_41e.pdf.

Eriksen, G.S., Alexander, J. (Eds.) 1998. *Fusarium* toxins in cereals—a Risk Assessment. Nordic Council of Ministers, TemaNord 502, Copenhagen, pp. 7–44.

National Research Council, 1983. Risk Assessment in the Federal Government: Managing the Process. NAS Press, Washington, DC, USA.

FAO/WHO, 2002. Pesticide residues in food 2002, FAO Plant Production and Protection Paper, 172, Rome, pp. 4–8.

Larsen, J.C., Richold, M., 1999. Report of Workshop on the Significance of Excursions above the ADI. Reg. Toxicol. Pharmacol. 30 (2), S2–S12.

Meky, F.A., Hardic, L.J., Evans, S.W., Wild, C.P., 2001. Deoxynivalenol-induced immunomodulation of human lympocyte proliferation and cytokine production. Food. Chem. Toxicol. 39 (8), 827–836.

Meky, F.A., Turner, P.C., Ashcroft, A.E., Miller, J.D., Qiao, Y.L., Roth, M.J., Wild, C.P., 2003. Development of a urinary biomarker of human exposure to deoxynivalenol. Food. Chem. Toxicol. 41 (2), 265–273.

Pestka, J., 2004. Cellular and Molecular Effects, Including Immunotoxic Effects. Toxicol Lett, this issue.

Pieters, M.N., Bakker, M., 2004. Probabilistic exposure models. Toxicol Lett, this issue.

Pieters, M.N., Freijer, J., Baars, A.J., Slob, W., 2001. Risk Assessment of Deoxynivalenol in Food. RIVM report 388802 022, Rijks Instituut voor Volksgezondheid en Milieu, Bilthoven, The Netherlands.

Renwick, A.G., et al., 2003. Risk characterisation of chemicals in food and diet. Food Chem. Tox. 41, 1211–1271.

Schothorst, R., van Egmond, H.P., 2004. Critical Assessment of Exposure—Report from the Scoop Project. Toxicol Lett, this issue.

Scientific Committee on Food, 1999. Opinion on Fusarium Toxins-Part 1: Deoxynivalenol DON) (expressed on 2 December 1999) http://europa.eu.int/comm/food/fs/sc/scf/out44_en.html.

Scientific Committee on Food, 2000. Opinion on Fusarium Toxins Part 4: Nivalenol. http://europa.eu.int/comm/food/fs/sc/scf/out185_en.pdf.

Scientific Committee on Food, 2001. Opinion on Fusarium Toxins, Part 5: T-2 toxin and HT-2 toxin. http://europa.eu.int/comm/food/fs/sc/scf/out88_en.pdf.

Scientific Committee on Food, 2002. Opinion on Fusarium Toxins. Part 6: Group evaluation of T-2 toxin, HT-2 toxin, nivalenol and deoxynivalenol. http://europa.eu.int/comm/food/fs/sc/scf/out123_en.pdf.

Schlatter, J., 2004. Toxicity data relevant to hazard characterization. Toxicol Lett, this issue.

Speijers, G.J.A., Speijers, M.H.M., 2004. Combined toxic effects. Toxicol Lett, this issue.

WHO, 1998. GEMS/Food Regional Diets. Regional Per Capita Consumption of Raw and Semi-processed Agricultural Commodities (WHO/FSF/FOS/98.3), Geneva.