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# TOXICITY AND RISKS WITH T-2 AND HT-2 TOXINS IN CEREALS

### ABSTRACT

The trichothecenes T-2 and HT-2 toxins have during recent years been found frequently in cereals grown in Europe. They are mainly produced by *Fusarium langsethiae*. High concentrations of the toxins are most commonly found in oats, but they are also detected frequently at lower concentrations in barley. Wheat is only rarely contaminated. Yearly surveys of T-2 and HT-2 toxins in oats from Northern Europe have shown that the occurrence and levels have increased from 2002, with very high levels in 2005-2007, followed by a decrease in 2008-2009.

Raw oats delivered to mills for processing to food have also been highly contaminated with T-2 and HT-2 toxins during the period 2006-2009. The processing of oats in the mills by sorting-sieving and dehulling reduce the toxin concentrations in the final food products, flakes and meals, with more than 80 % even at high levels in the raw oat. The concentrations of the toxins in the by-products from the process are instead increased. The by-products are mainly used as feed components.

The toxic effects of T-2 and HT-2 toxins in animals and the toxicological information used in the risk evaluations are briefly described. Risk evaluations of the toxins in cereals for human consumption have been conducted by both EU-Scientific Committee on Food and by JECFA in 2001. Both evaluations resulted in the same temporary tolerable daily intake (t-TDI) for the sum of T-2 and HT-2 toxins. The group TDI for T-2 and HT-2 toxins, alone or in combination, became 60 ng/kg bw and day.

The intake of T-2 and HT-2 toxins through oats is calculated from median concentrations in oat products and median consumption data from Norway. The intake was found to be 1.5-5.4 % of the t-TDI.

The toxic effects studied or expected in farm animals, horses and ruminants, consuming high amounts of oat in their feed are described and discussed.

Key words: Fusarium langsethiae, HT-2 toxin, oats, T-2 toxin, toxin contamination, toxicity, risk

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## INTRODUCTION

Cereal plants are worldwide infected with different *Fusarium* species and some of them e.g. *F. graminearum*, *F. culmorum* are associated with plant diseases like Fusarium Head Blight and grain contamination with toxins. Other Fusarium species e.g. *F. poae*, *F. langsethiae* do not produced clear pathogenic symptoms but may still produce toxins.

The trichothecene deoxynivalenol mainly produced by *F. graminearum* is the most frequently found fusarium toxin and present at the highest concentrations in especially wheat. The more toxic trichothecenes T-2 and HT-2 toxins have during recent years been found also frequently in cereals grown in Europe (Edwards *et al.* 2009, Pettersson *et al.* 2008). They are mainly associated with *F. langsethiae*, but may be produced also by *F. sporotrichioides* in cereals from East and South Europe. T-2 and HT-2 toxins have most frequently been found at highest concentrations in oats followed by barley. Wheat is much less contaminated.

Tricothecenes in cereals were risk evaluated by the EU Scientific Committee on Food (SCF 2001) and JECFA (Joint FAO/WHO Expert Committee on Food Additives) in 2001. a combined temporary tolerable daily intake (t-TDI) of 0.06  $\mu$ g/kg body weight and day was established for T-2 and HT-2 toxins, since T-2 toxin is readably converted into HT-2 toxin after consumption.

The European Union has introduced maximal tolerable levels of deoxynivalenol in cereals intended for food and recommendation on guidance levels in feed (EC 2006a,b). There are currently no legal limits for T-2 and HT -2 toxins in food or feed, although the intention to introduce such is indicated in the legislation. The time table for introduction has been prolonged, partly due to the high occurrence of the toxins in oats.

This paper will give a review of the occurrence of T-2 and HT-2 toxins in European cereals, effect of processing, their toxicity and risks for human and animals.

#### OCCURRENCE

Surveys of T-2 and HT-2 toxins in European cereals during the 1990-ties as reported by SCOOP 2003 and JECFA 2001 showed that the toxins occurred most frequently in oats followed by barley and maize. Wheat was much less contaminated. The mean levels for the sum of T-2 and HT-2 toxins were generally relatively low (< 100  $\mu$ g/kg) although some max values in certain oat samples exceeded 1000  $\mu$ g T-2+HT-2/kg. The surveys of trichothecenes in cereals continued in Scandinavia and started in UK during the period 2000 to 2009. Results from the surveys of T-2 and HT-2 toxins in oats are presented in Table 1. High and increasing levels of T-2 and HT- 2 toxins were found in oats from Scandinavia and UK in 2002 to 2006. Thirty-three to 44 % of the samples from UK, Finland, and Sweden exceeded 500  $\mu$ g T-2+HT-2/kg during at least one year. Median levels above 200  $\mu$ g/kg were recorded and max concentrations up to 9990  $\mu$ g/kg were found. The levels decreased in oats from all survey countries during the period 2007-2009.

T-2 and HT-2 toxins in surveys of oats 2000-2009. (after Pettersson 2010)

Table 1

|         | Country | Number<br>ountry of Sam-<br>ples | Percen-      | Percentage of                  |    | Mean    | Median  | Max     |                            |
|---------|---------|----------------------------------|--------------|--------------------------------|----|---------|---------|---------|----------------------------|
| Year    |         |                                  | >10<br>[ppb] | 10 >50 >500<br>bb] [ppb] [ppb] |    | [µg/kg] | [µg/kg] | [µg/kg] | Reference                  |
| 1994    | Sweden  | 34                               |              | 24                             | 3  | 81      | 25      | 871     | Pettersson 2000            |
| 1000    | Sweden  | 80                               |              | 18                             | 0  | 57      | 20      | 390     | Pettersson 2000            |
| 1996    | Norway  | 14                               | 100          | 50                             |    | 190     |         | 718     | Langseth et al. 2001       |
| 1996-98 | Norway  | 178                              | 70           | 33                             |    | 108     |         | 1260    | Langseth & Rundberget 1999 |
|         | Finland | 51                               |              | 4                              | 2  | <50     | <50     | 856     | Hietaniemi et al 2004      |
| 1997    | Sweden  | 84                               |              | 20                             | 0  | 39      | 15      | 216     | Pettersson 2000            |
|         | Norway  | 84                               | 71           | 38                             |    | 132     |         | 1260    | Langseth et al. 2001       |
|         | Finland | 52                               |              | 2                              | 0  | <50     | <50     | 116     | Hietaniemi et al 2004      |
| 1000    | Finland | 13                               |              | 15                             | 0  | 20      | 10      | 116     | Eskola et al 2000          |
| 1998    | Sweden  | 33                               |              | 27                             | 0  | 33      | 15      | 134     | Pettersson 2000            |
|         | Norway  | 80                               | 63           | 18                             |    | 68      |         | 585     | Langseth et al. 2001       |
|         | Finland | 59                               |              | 7                              | 0  | <50     | <50     | 240     | Hietaniemi et al 2004      |
| 1999    | Finland | 10                               |              | 0                              | 0  | 10      | 10      | 10      | Yli-Mattila et al 2004     |
|         | Norway  | 20                               |              | 85                             | 0  | 117     |         | 330     | Langseth et al. 2001       |
|         | Finland | 25                               |              | 36                             | 8  | 137     | 25      | 1369    | Hietaniemi 2006            |
| 2000    | Norway  | 22                               |              | 73                             | 5  | 86      | 53      | 564     | SCOOP 2003                 |
| ••••    | Finland | 37                               |              | 27                             | 0  | 59      | 25      | 273     | Hietaniemi 2006            |
| 2001    | Norway  | 24                               |              | 0                              | 0  | 10      | 10      | 10      | SCOOP 2003                 |
|         | Finland | 30                               |              | 37                             | 0  | 78      | 38      | 427     | Hietaniemi 2006            |
| 2002    | UK      | 92                               | 85           | 70                             | 16 | 311     | 106     | 4844    | Edwards 2006               |
|         | Finland | 30                               |              | 63                             | 13 | 305     | 116     | 1647    | Hietaniemi 2006            |
| 2003    | UK      | 104                              | 90           | 69                             | 33 | 727     | 204     | 9990    | Edwards 2006               |
|         | Finland | 30                               |              | 57                             | 10 | 282     | 104     | 2850    | Hietaniemi 2006            |
| 2004    | Norway  | 56                               |              | 70                             | 0  | 106     | 86      | 334     | Clasen 2006                |
|         | UK      | 128                              | 94           | 80                             | 24 | 500     | 202     | 6997    | Edwards 2006               |
|         | Finland | 60                               |              | 63                             | 33 | 440     | 186     | 3500    | Hietaniemi 2006            |
|         | Sweden  | 41                               |              | 61                             | 17 | 255     | 90      | 1165    | Pettersson 2006            |
| 2005    | Norway  | 126                              |              | 87                             | 13 | 283     | 180     | 2041    | Clasen 2006                |
|         | Denmark | 18                               | 100          | 94                             | 6  | 312     | 221     | 2560    | Biselli 2006               |
|         | IJК     | 134                              | 97           | 88                             | 44 | 694     | 403     | 3188    | Edwards 2006               |

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| Year | Country | Number<br>ry of Sam-<br>ples | Percen-      | Percentage of |               | Mean    | Median  | Max     |                 |  |
|------|---------|------------------------------|--------------|---------------|---------------|---------|---------|---------|-----------------|--|
|      |         |                              | >10<br>[ppb] | >50<br>[ppb]  | >500<br>[ppb] | [µg/kg] | [µg/kg] | [µg/kg] | Reference       |  |
| 2007 | Finland | 59                           |              | 53            | 5             | 163     | 47      | 1283    | Hietaniemi 2007 |  |
|      | Sweden  | 71                           |              | 90            | 44            | 465     | 376     | 1416    | Pettersson 2007 |  |
| 2006 | Norway  | 102                          |              | 78            | 9             | 218     | 145     | 1675    | Clasen 2006     |  |
|      | UK      | 100                          | 97           | 96            | 43            | 795     | 404     | 6261    | Edwards 2007    |  |
|      | Finland | 80                           |              | 53            | 5             | 121     | 64      | 863     | Hietaniemi 2007 |  |
| 2007 | Sweden  | 58                           |              | 91            | 10            | 255     | 90      | 1165    | Pettersson 2008 |  |
| 2007 | Norway  | 32                           |              | 94            | 6             | 217     | 177     | 980     | Clasen 2008     |  |
|      | UK      | 103                          |              | 77            | 18            | 438     | 169     | 8399    | Edwards 2008    |  |
|      | Finland | 80                           |              | 38            | 5             | 100     | 32      | 1932    | Hietaniemi 2009 |  |
| 2008 | Sweden  | 70                           |              | 34            | 0             | 57      | 34      | 493     | Pettersson 2009 |  |
| 2008 | Norway  | 33                           |              | 64            | 0             | 62      | 55      | 145     | Clasen 2009     |  |
|      | UK      | 90                           |              |               | 7             | 120     | 47      | 1190    | Edwards 2009    |  |
| 2009 | Finland | 80                           |              | 39            | 4             | 85      | 25      | 1020    | Hietaniemi 2010 |  |
|      | Sweden  | 27                           |              | 33            | 4             | 82      | 35      | 886     | Pettersson 2010 |  |

T-2 and HT-2 toxins in surveys of oats 2000-2009. (after Pettersson 2010) — continued

Table 1

The European Breakfast Cereal Association (CEEREAL) has analyzed T-2 and HT-2 toxins in 235 samples of raw oats delivered to their mills during 2006-2009 (Pettersson 2010). The overall median level was only 44  $\mu$ g T-2+HT-2/kg with a max value of 841 $\mu$ g/kg in 2006. The decrease in the levels during 2008-2009 compared to 2006-2007 was clear.

Barley and wheat have also been analyzed for T-2 and HT-2 toxins in Scandinavia, UK and France during several years in the period 2000-2009. Concentrations above 50  $\mu$ g T-2+HT-2/kg have only rarely been detected in wheat. Barley samples above that level occurred more frequently, but most positive samples had a concentration below. In the French surveys of spring barley such low levels were frequently detected (Orlando *et al.* 2010). The adjusted mean concentrations for the years 2006-2008 were between 19 and 22  $\mu$ g T-2+HT-2/kg. The toxins were much less frequently detected in winter barley although fewer samples had been analyzed.

All oats for human consumption are processed in mills. Oats are cleaned by screening, dehulled, sorted and flaked or milled. T-2 and HT-2 toxin concentration in the final products used for food are reduced by an average of 80% during especially the dehulling step. The effect of processing on the toxin levels in oats from UK mills are in detail described by Scudamore *et al.* 2007. The toxin levels in the by-products (husks, debris, small kernels) often used for feed will instead increase by on an average up to 3 times compared to the raw oats.

The CEEREAL has also analyzed T-2 and HT-2 toxins in the oat-flakes and oat by -products obtained in their mills during 2005-2009 (Pettersson 2010). The concentra-

tions in the raw oats, oat-flakes and oat by-products from the mills are given in Table 2. The mean and median concentrations in oat-flakes decrease by 81 and 73 % respectively compared to raw oats and increased by 307 and 345 % in the oat-byproducts.

Table 2

|                | Number          | Percentage of samples |               |               |                | Maar              | Madian            | 00 <sup>th</sup> 0/ :1- | Mari    |
|----------------|-----------------|-----------------------|---------------|---------------|----------------|-------------------|-------------------|-------------------------|---------|
| Product        | of sam-<br>ples | >50<br>[ppb]          | >200<br>[ppb] | >500<br>[ppb] | >1000<br>[ppb] | - Mean<br>[µg/kg] | Median<br>[µg/kg] | 90 %1e<br>[µg/kg]       | [µg/kg] |
| Oats raw       | 235             | 43                    | 12            | 2             | 0              | 96                | 44                | 212                     | 841     |
| Oat flakes     | 435             | 8                     | 0             | 0             | 0              | 18                | 12                | 41                      | 197     |
| Oat by-product | 208             | 86                    | 46            | 15            | 10             | 295               | 152               | 663                     | 1711    |

T-2 and HT-2 toxins in oats and oat products from European mills in the CEEREAL study 2005-2009. (after Pettersson 2010)

# TOXICITY

T-2 and HT-2 toxins exhibit their toxicity mainly by inhibiting DNA, RNA and protein synthesis, the latter at the ribosomal level. The toxins are therefore highly cytotoxic and more toxic compared to the other trichothecenes partly due to their more lipophilic character and membrane permeability. T-2 toxin is rapidly converted into HT-2 toxin after ingestion by animals. The toxicity of T-2 and HT-2 toxins in animals is thus considered to be similar.

Several studies in mice and rats show that T-2 toxin causes cytotoxicity and proliferative changes in the oesophagus- and forestomach epithelium. Several tests for genotoxicity *in vitro* and in rodents *in vivo*, especially for clastogenic effects, were positive for T-2 and HT-2. There is, however, limited evidence for carcinogenicity in experimental animals. It induced hepatocellular- and pulmonary adenomas in male mouse (Schiefer *et al.* 1987).

The most important toxicity studies identified by the EU Scientific Committee on Food (SCF, 2001) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2001) in their evaluation of T-2 and HT-2 toxicity are given in Table 3. The LOAEL (Lowest Observed Adverse Effect Levels) or NOAEL (No Observed Adverse Effect Levels) are given for the critical effects. Both Committees, the JECFA and the SCF, used the haematotoxicity and immunotoxicity of T-2 toxin in the subacute toxicity study in pigs by Rafai *et al.* 1995a as the bases for their safety assessment. There are deficiencies in the toxicity studies, e.g study duration, pair feeding of control animals, comparative studies on metabolism and toxicokinetics. To account for this and the use of a LOAEL, the Committees included an extra uncertainty factor of 5, giving an overall uncertainty factor of 500. a temporary or provisional maximal Tolerable Daily Intake (t-TDI or PMTDI) of 0.06  $\mu$ g/ kg bodyweight and day was thus established for the sum of T-2 and HT-2 toxins.

| Study                                    | Critical effect  | NOAEL/LOAEL<br>[mg/kg b.w./Day] | Reference                     |  |
|--|--|---------------------------------|-------------------------------|--|
|  | Pulmonary adenomas   | 0.23 (NOAEL)                    |                               |  |
| Mouse, 16 months                         | Hepatocellular adenomas  | 0.23 (NOAEL)                    | Schiefer et al. 1987          |  |
|  | Forestomach epithelial hyperplasi  | 0.23 (NOAEL)                    |                               |  |
| Rat, 4 week                              | Forestomach epithelial hyperplasi  | 0.5 (NOAEL)                     | Ohtsubo and Saito             |  |
| Mouse, 5 days                            | Thymus athrophy, decreased number of   | 0.75 (LOAEL)                    | Smith et al. 1994             |  |
| Pig, 3 weeks (subacute)                  | Reduced number of leukocytes, lym-<br>phocytes and antibody production<br>against horse globulin. Decrease in size | 0.03 (LOAEL)                    | Rafai <i>et al.</i> 1995      |  |
| Monkey (15 days by                       | Leukopenia   | 0.1 (LOAEL)                     | Rukimini et al.               |  |
| Mouse, CD-1, two<br>generations. No dose | Embryo- or foetotoxicity   | 0.45 (NOAEL)                    | Rosseaux and<br>Schiefer 1987 |  |
| Rat, single dose                         | Neurotoxicity  | 0.4 (NOAEL)                     | Sirkka <i>et al.</i> 1992     |  |

Critical Toxicology studies on T-2 toxin identified by SCF in 2001. (after Slatter 2004)

The toxicity of T-2 and HT-2 toxins in farm animals was evaluated by Eriksen and Pettersson 2004. The lowest effect level in feed for certain toxic effects in major feeding studies with pigs and chickens are given in Table 4. Guidance values for the highest T-2 and HT-2 concentrations in feed for pigs and chicken was suggested to 0.2 and 0.5  $\mu$ g/kg respectively.

Table 4

Table 3

|         |                                     | 1.0                            |  |  |  |
|---------|-------------------------------------|--------------------------------|--|--|--|
| Animals | Lowest Effect<br>level              | Toxic Effect                   | Reference  |  |  |
| Pig     | 0.5                                 | Reduced immunedefence          | Rafai et al. 1995b   |  |  |
|         | 1-2                                 | Reduced growth and feed intake | Rafai <i>et al.</i> 1995a, Friend <i>et al.</i><br>1992, Weaver <i>et al.</i> 1978 |  |  |
| Chicken | 0.4-1                               | Mucosa erosion                 | Wyatt et al. 1972, 1973  |  |  |
|         | 2 Reduced feed consumption and grow |                                | Wyatt et al. 1972, 1973  |  |  |

Lowest effect level of T-2 toxin in feed for pigs and chicken.

There are hardly any reports on toxic effects in ruminants fed T-2 and HT-2 toxins in controlled studies. This may be due to that trichothecenes including T-2 and HT-2 toxins are rapidly degraded and detoxified by mi-

croorganisms in the rumen. They are deacetylated and de-epoxidated. The removal of the epoxide is the main detoxification of trichothecenes. De-epoxidation activities have also been found in faeces from pigs and horses (Eriksen *et al.* 2002; Pettersson *et al.* 2007), but it is unclear if this reaction in the lower part of the gastro-intestinal tract may have an influence on the eventual toxic effects.

Horses may be highly exposed to T-2 and HT-2 toxins but there are only few case reports on their eventual toxic effects in horses. Most cases are from East Europe but T-2 toxin has also been the cause of bean-hull poisoning of horses in Japan. Toxic effects described are CNS toxicity, muscle contraction, tachycardia and colic. The exposure of trotter horse to T-2 and HT-2 toxins through oats has been studied in Sweden (Pettersson *et al.* 2007). Horses consuming an average of 2.6 mg T-2+HT-2 per day were compared with a group consuming 0.7 mg toxins per day. No clear effects were seen on health and performance of the horses.

### RISKS

Estimation of human intake of T-2 and HT-2 toxins through oats and comparison with the established t-TDI can provide information on the risks with the toxins in food oats. JECFA (2001) made intake calculations for the trichothecenes based on the toxin database available for each cereal at that time and different cereal consumption information. The calculated intakes were high for many population groups and the intake for the sum of T-2 and HT-2 toxins exceeded the combined t-TDI in most high cereal consumption groups. The toxin portion from oats was about 50% of the intake. The mean concentration used for oats in the calculations was a weight mean (21  $\mu$ g T-2/kg, 35  $\mu$ g HT-2/kg) of all European analysis on unprocessed oats. This is not an appropriate concentration value to use in the calculations since unprocessed oats are not consumed and processing decrease the toxin concentrations with more than 80%.

The median concentration of T-2 and HT-2 toxins in oat-flakes for the year 2005-2009 from the study by CEEREAL are more correct to use. This concentration has been used together with the detailed Norwegian oat consumption data for the calculation of intake in Table 5. Oat consumption in Norway is relatively high and a median consumption has been used in the calculations. The intake of T-2 and HT-2 toxins from oats is then 1.5-5.4 % of the t-TDI depending on groups and much lower than in the JECFA calculations. If the intake is calculated for high oat consumers (95<sup>th</sup> percentile consumption) and high toxin concentration (90<sup>th</sup> percentile) in the oat-flakes, the toxin intake will become 48-77 % of the t-TDI.

About 75 % of the European oat crop is used in animal feed. Oats are mainly used in feed for ruminants and horses. It is less popular in feeds for pigs and

poultry due to the relative high fibre content and low energy value. Oat byproducts are only used in horse and ruminant feed.

Table 5

|             | D 1  |                 | Median Consumption |            |             |          |  |  |
|-------------|------|-----------------|--------------------|------------|-------------|----------|--|--|
| Population  | Body | concentration – | Grain              | Toxin      |             |          |  |  |
| group       | [ko] |                 | [g/person          | [ng/person | [ng/kg b.w. | % of TDI |  |  |
|             | [*6] |                 | per day]           | per day]   | per day]    |          |  |  |
|             |      |                 | Children           |            |             |          |  |  |
| 6 years     | 23   | 12              | 6.2                | 74.4       | 3.23        | 5.4      |  |  |
| 10 years    | 35   | 12              | 8.2                | 98.4       | 2.81        | 4.7      |  |  |
|             |      |                 | Males              |            |             |          |  |  |
| 16-29 years | 75   | 12              | 7.5                | 90         | 1.20        | 2.0      |  |  |
| 30-59 years | 83   | 12              | 7.6                | 91.2       | 1.10        | 1.8      |  |  |
| 60-79 years | 79   | 12              | 6.5                | 78         | 0.99        | 1.6      |  |  |
|             |      |                 | Females            |            |             |          |  |  |
| 16-29 years | 63   | 12              | 6.3                | 75.6       | 1.20        | 2.0      |  |  |
| 30-59 years | 65   | 12              | 5.8                | 69.6       | 1.07        | 1.8      |  |  |
| 60-79 years | 69   | 12              | 5.1                | 61.2       | 0.89        | 1.5      |  |  |

Intake of T-2 and HT-2 toxins from oats calculated on consumption data from Norway. Median consumption and median toxin concentration from CEEREAL study

Oats with median T-2 and HT-2 toxin concentrations (Survey mean 90  $\mu$ g/kg, CEEREAL 42  $\mu$ g/kg) can be used in feed to pigs and poultry without restrictions due to toxin content and risk for exceeding feed guidance levels. The oat component in their feeds rarely exceeds 50% of the diet. Oats containing high toxin levels equal to the 90<sup>th</sup> percentile (208  $\mu$ g/kg) in the CEEREAL study could also be used, but oats with concentrations above 1000  $\mu$ g T-2+HT-2/kg may cause adverse effects.

In adult ruminants even the highest T-2 and HT-2 toxin concentrations in oats are expected to be degraded and detoxified by the rumen microbes. The highest toxin concentrations may have a local contact effect causing erosions on the muzzle and in the mouth. This has however not been described.

Athletic or working horses may be fed up to 6 kg oats per day in addition to the roughage. If oats with a median toxin concentration (90 or 42  $\mu$ g/kg) is used the daily intake will be only 0.25-0.54 mg/day or calculated on a body weight of 500kg give 0.5-1.1  $\mu$ g/kg b.w. and day. The lowest adverse effect level of T-2 and HT-2 toxins in horses is not known, but this daily amount will probably not cause adverse effects. Oats with T-2 and HT-2 concentrations above 1000  $\mu$ g/kg will give a daily consumption of more than 6 mg/day or more than 12  $\mu$ g/ kg b.w. and day. These amounts are expected to cause toxic effects in the horses, although it was not noticed in the study on trotter horses in Sweden. An explanation could be the degradation of trichothecenes in intestinal and feces content of horses fed oats. a local cytotoxic contact effects caused by high toxin concen-

trations could also be expected in the muzzel, mouth, stomach and upper intestine of the horses. T-2 and HT-2 toxins are highly cytotoxic and cause cell death at concentrations from 0.3-20 ng/ml in cell culture studies.

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