codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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POSITION PAPER ON ZEARALENONE

REQUEST FOR COMMENTS AND INFORMATION

Governments and interested international organizations wishing to submit comments on the following Position Paper on Zearalenone are invited to do so **no later than 15 January 1999** as follows: Ms. S.P.J. Hagenstein, Netherlands Codex Contact Point, Ministry of Agriculture, Nature Management and Fisheries, P.O. Box 20401, 2500 EK The Hague, The Netherlands (Telefax: +31 70 378.6141; E-mail: s.p.j.hagenstein@mkg.agro.nl), with a copy to the Chief, Joint FAO/WHO Food Standards Programme, FAO, Via delle Terme di Caracalla, 00100 Rome, Italy.

BACKGROUND

1. The 30th Session of the Codex Committee on Food Additives and Contaminants (CCFAC) decided to circulate the position paper presented (CX/FAC 98/18) for comment and consideration at its 31st meeting (ALINORM 99/12, paras. 86-88). The position paper previously prepared by Norway is attached.

INTRODUCTION

2. Zearalenone is an important mycotoxin in temperate and warm regions of the world. It is produced by fungi of the genus *Fusarium*. The toxin occurs mainly in maize, but also in lower concentrations in rice, wheat and barley, and malt. Zearalenone has been detected in beer from some countries in southern Africa, while in a German survey, zearalenone was not detected in any of the 42 samples (1,

3. The explanation for this difference may be that maize is used in the production of beer in the African countries, while barley is more often used in Europe. In addition, the toxin has been detected in cereal products like flour and beer, in soybeans and products thereof (1, 3, 4). Occurrences in mixed feeds associated with hyperoestrogenism and other problems in swine and cattle in various countries have been reported.

4. Fusarium taxonomy is complex and classification is a difficult task. Because of the complexity of the taxonomy, many isolates have been misidentified. Many earlier reports have been reviewed and most

errors have been corrected. Zearalenone is now considered to be produced by *F. graminearum, F. culmorum, F. cerealis, F. equiseti*, and *F. semitectum.* Reports of production of zearalenone by other species have been questioned (5, 6, 7).

5. Fungi of the genus *Fusarium* infect cereals in the field. Toxin production mainly takes place before harvesting, but may also occur post harvest if the crop is not handled and dried properly.

6. Zearalenone is a resorcyclic acid lactone which is chemically described as 6-(10-hydroxy-6-oxo-trans-1-undecenyl)- b -resorcyclic acid lactone. In mammals, the keto group at C-6 is reduced to two stereoisomeric metabolites of zearalenone (a and b isomers). These metabolites are also produced by the fungi, but in much lower concentrations than zearalenone. Another compound with structural similarity is zeranol, which is used as a growth promoter. This compound is only distinguished from zearalenone by the lack of a C1-C2 double bond (3, 4).

7. Various analytical methods for identification and quantification of zearalenone have been developed. Early methods were generally based on thin-layer chromatography (TLC). Today, methods using HPLC with fluorescence detection are most common, although UV and electrochemical detection are also used (3, 7, 8). ELISA kits for determination of zearalenone are also available.

TOXICOLOGICAL EVALUATIONS

8. Zearalenone has not been evaluated by JECFA. The International Agency for Research on Cancer (IARC) evaluated the carcinogenic potential of zearalenone and concluded that there was limited evidence of carcinogenicity of zearalenone in experimental animals and that zearalenone was not classifiable according to their human carcinogenicity criteria (Group 3) (4). In a 2 year US NTP-study a statistical significant increase in hepatocellular adenomas was seen in female mice. Furthermore a statistically significant increase in pituitary adenomas and a small, non-statistically significant increase in pituitary carcinomas, were found in mice, but not in rats. (9). An increase in the incidence of pituitary adenomas in rats would however be difficult to detect due to the high natural incidence in this species. No carcinogenic effects were found in another 2 year study with rats (10). Subsequently, formation of DNA-adducts has been found in mice, but not in rats, after a single exposure to zearalenone (11, 12). This corresponds well with the results from the two-year US NTP study showing a carcinogenic effect of zearalenone in mice, but not in rats. Altogether, this indicates that zearalenone may have a species-dependent carcinogenic effect. No information about formation of DNA-adducts in humans is available.

9. An extensive review of the occurrence and toxicity of zearalenone and risk assessment was made in Canada in 1987 (3). The risk assessment concluded that oestrogenic and possible carcinogenic effects are the critical effects of zearalenone. Deriving a TDI from the possible carcinogenic effect using a mathematical linear extrapolation with a risk level of $1{:}10^{-6}$ would lead to a virtually safe dose of 0.05 µg/kg bw. per day. In a study exposing monkeys to zearalenol, which has a higher oestrogenic activity than zearalenone, a no hormone effect level of 50 µg/kg b.w per day was found. Deriving a TDI from this study, using a safety factor of 500 due to the uncertainties in the animal model, lead to a estimated safe intake of 0.10 µg/kg b.w per day. After an overall evaluation, a temporary TDI of 0.1 µg/kg b.w. per day was proposed, based on an estimated no hormonal effect level and a virtually safe dose with respect to carcinogenicity estimated with a conservative model with a risk level of $1{:}10^{-6}$.

10. A Nordic expert group considered the Canadian TDI as still valid since no relevant additional *in vivo* information on the dose-effect relations of hormonal effects and no more data concerning the possible carcinogenic effect of zearalenone were available (7).

11. Zearalenone or the similar growth promoter zearalanol was suspected to be the causative agent in an epidemic of precocious pubertal changes in young children in Puerto Rico (13, 14). Zearalenone or metabolites were detected in blood plasma. The authors reported high levels of the growth promoter zearalanol in locally produced meat, but later studies by FDA failed to detect any oestrogenic growth

promoter. Natural sources of oestrogen-acting compounds, like plant metabolites or mycotoxins as a cause of the epidemic have not been ruled out.

DIETARY INTAKES

12. Due to the rapid biotransformation and excretion of zearalenone, the dietary intake from meat and products thereof is probably of little significance. Only minimal transmission of zearalenone to milk of dairy cows has been found after exposure to low doses of zearalenone (15) and there is no evidence of zearalenone in milk intended for human consumption. Nor has zearalenone been reported in eggs from commercial production. It is therefore assumed that the main dietary sources of zearalenone are cereals and products thereof, while meat, egg and milk are probably of less significance.

13. The Canadian daily intake of zearalenone from maize, and maize-based cereals has been estimated to be 0.005 - 0.087 µg/kg b.w. for 12 - 19 year-old males, which was the highest consumption group. An additional intake from popcorn was estimated to be 0.001 - 0.023 µg/kg b.w. (3). A theoretical intake of zearalenone of 0.027 - 0.066 µg/kg b.w. from milk was estimated. These estimates were based on estimated concentrations of zearalenone and not analytical data. Later studies have demonstrated that only minimal transmission of zearalenone to milk of dairy cows occur under exposure to realistic levels of zearalenone (15). Intake from cereals other than maize was not estimated.

14. The dietary intake of zearalenone from cereals and products thereof in the Scandinavian countries was preliminary estimated to be 0.02 - 0.04 µg/kg b.w. per day (7). However, the data used in these estimations were rather old, and no detailed intake calculations were made.

MAXIMUM LIMITS FOR ZEARALENONE

15. No international maximum limit for zearalenone in foodstuff exists. Eight countries have specific regulations, ranging from 30 to 1000 µg/kg, for zearalenone. The limits apply to either specific foodstuffs or all food (16). No barriers to international trade have been reported.

CONCLUSIONS AND RECOMMENDATIONS

16. The preliminary intake calculations presented in the report by the Nordic Council of Ministers indicate that further action is to be taken. It is suggested that improved intake calculations are made, based on quality-controlled data on occurrence and detailed intake estimates of maize and other risk products.

17. It is recommended that zearalenone should be evaluated by JECFA. Together with the improved intake estimates, a JECFA evaluation would be essential when considering if any further action is needed to reduce risks associated with dietary intake of zearalenone.

18. The present position paper on zearalenone in food leads to the following recommendations:

a) The best way to protect the consumers from the toxic effects of zearalenone is to reduce the fungal infection of cereals and toxin production as much as possible by

   i) identifying the critical points where the fungi infect the cereals and produce zearalenone during the production of cereals

   ii) including quality control programmes in agricultural production

   iii) improving training of all persons involved in production of cereals

   iv) supporting research on methods and techniques to prevent fungal contamination in the field and during storage

b) It is recommended that Codex should include zearalenone in a code of practice aimed at reducing the levels of certain mycotoxins in cereals.

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