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«TRAINING ACTIVITIES ON FOOD CONTAMINATION CONTROL AND MONITORING WITH SPECIAL REFERENCE TO MYCOTOXINS»

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CARCINOGENESIS CAUSED BY MYCOTOXINS

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Mycotoxins, including aflatoxins (at least some of them), are characterized not only by potent toxic, but also by carcinogenic properties.

Likewise all other known chemical carcinogens, carcinogenic mycotoxins possess two specific properties: they are toxic and they induce a necrosogenic effect on sensitive cells. Carcinogenic mycotoxins are the products of lower microscopic fungi, thus, the toxicogenic and carcinogenic strains of the above fungi infect and contaminate food produce as if in its "natural" environment: in the field, during storage, etc. Common occurrence of these microscopic mold fungi in nature creates a possibility of the existence of a "natural" and considerable contamination of the food raw material, food products and animal fodders. All this can represent a pathway for the penetration of carcinogenic substances - mycotoxins into the organism of man (or livestock animals).

The pathogenic strains of Aspergillus flavus are known to produce aflatoxins. At present, four toxic metabolites of Aspergillus flavus - aflatoxins B_1, B_2 and G_1, G_2 have been identified. Originally, these aflatoxins were isolated from peanuts. Nowerdays, they are isolated from many food and fodder products. Another two metabolites - aflatoxins M_1 and M_2 have been isolated from mammalian milk.

The detailed information on the chemical structure, phy-

aical, chemical, microbiological and toxic properties of aflatoxins, including aflatoxin B_1, is given in other lectures of the course.

How can we define the carcinogenic activity of the above mycotoxins? A group of Experts of the International Agency for Research on Cancer in Lyon discribed the following group of carcinogenic metabolites of the lower fungi (Table 1).x/

Aflatoxins are most adequately studied. Based on multiple investigations, the existing pattern of cancerogenecity related to aflatoxins can be formulated in the following way: "Aflatoxins are carcinogenic for mice, rats, fishes, ducks, some primates; penetrating the organism through various routs, aflatoxins induce the development of hepatic, renal and colon tumors. Epidemiological studies showed a positive correlation between the rate of aflatoxin content in food diets of studied human populations and the incidence of primary liver cancer. The above (epidemiological) studies were specially organized to confirm the assumed correlation between aflatoxins consumed with food and the development of primary liver cancer. No observations, however, proving the relationship between a higher risk of liver cancer and the consumption of aflatoxins with food, were recorded in individuals (IARC, 1979).

A characteristic feature of aflatoxin B_1 as a blastomoge-

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x/ IARC (1976) Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, vol. 10.

nic agent consists in the fact that this very potent hepatocarcinogen is capable, however, of inducing only hepatocellular carcinomas. In other words, of many various tissues only the epithelial cells of hepatic cords, i.e. hepatocytes, are the target for the carcinogenic effect of aflatoxin B_1. P. Newberne and colleagues experimentally showed that a single dose of aflatoxin B_1 administered to young mice can cause, after more or less long-term latent period, the development of malignant hepatomas. The sensitivity of hepatic rat cells to the carcinogenic effect of aflatoxin B_1 is so high that one can hardly speak about the minimal effective dose for these animal species as, for example, the concentration of aflatoxin in the amount of 1 ug/kg of diet was found to be sufficient to induce hepatomas in two and precancerous hyperplasia in seven rats out of 22 (Wogun, Newberne et al.). If the diet of the experimental rats contained aflatoxin B_1 in the amount of 100 ug/kg, hepatic and renal neoplasms developed in 100% of the animals (ibid.). While aflatoxin B_1 represents a very powerful hepatic carcinogen, not all warm-blooded animals are equally sensitive to it. Mice, for example, display high resistance and do not develop either hepatic or other tumors after receiving this carcinogen per os. Intraperitoneally-introduced aflatoxin B_1 is known to induce lung adenomas in mice. This should be remembered as well as the fact that adenomatous changes in the lungs of mice and rats can develop due to infectious diseases.

Differentiating animal species by the degree of their sensitivity to the toxic effect of aflatoxin B_1 will not

change, on the whole, in relation to the cercinogenic effect of this aflatoxin. High sensitivity is observed in ducklings, young turkeys, young male rats, some fish species (especially Salmonidae), piglets, primates; mice and sheep were found to be resistant.

And what is the human sensitivity to toxic and carcinogenic effects of aflatoxins and of aflatoxin B_1, in particular?

It was only natural that from the outset of their aflatoxin studies the investigators were particularly concerned with the problem of primatial sensitivity to acute, chronic and carcinogenic effects of aflatoxins. The initial notions about the resistance of the primates has been gradually changed, and, at present, sufficiently typical clinical and pathoanatomical symptoms of acute and chronic intoxications caused by orally-administered aflatoxin B_1, have been ascertained. Experiments on primates demonstrated that aflatoxins were also powerful hepatotropic toxins for these animal species, capable of inducing massive necroses in the parenchyma of the liver. In cases of sublethal injury such necroses were accompanied by considerable proliferations of tiny biliary ducts, by cholangiofibrosis, development of the nodes of the hepatic cellular hyperplasia, and by replacement fibrosis. Such changes also appear in the liver of the experimental animals as a result of the administration of such well known hepatocarcinogens as ethionine, ethyl-analogue of methionine, and azocarcinogens. Nevertheless, the question of the possibility of inducing hepatic cancer in primates by the administration of aflatoxins into the stomach, remained for some time un-

solved. By the present time, a number of scientific papers has been published showing that in cases of sufficiently durable delivery of aflatoxin B_1 or mixtures of several aflatoxins into the organisms of experimental primates, hepatic and renal neoplasms can develop in some of the animals if the duration of the experiment is long enough (5 and more years). An important factor should be noted: in a number of experimental studies these single cases when hepatic cancer developed in primates receiving aflatoxins were "caught" (i.e. not overlooked) by the investigators several years later when the animals were fed with normal diet void of aflatoxin effect. In such cases the latent period of hepatic cancer induction in primates reached 6 (!) years.

Thus, the existing data indicate the sensitivity of primates to the carcinogenic effect of aflatoxins, and that like in other animals, their parenchymatous hepatic tissue and the epithelial cells of hepatic cords represent the target organs for the carcinogenic effect of aflatoxins. Naturally, this factor is of a special significance in the estimation of the carcinogenic risk of aflatoxins to man. The above factor is extremely important, however, is not the decisive one. Carcinogenic aflatoxins are not by far equally damaging even for animals of related species. We have already noted a sharp dissimilarity in sensitivity of rats and mice. While hepatic cancer can be induced in rats by aflatoxin B_1 in 100% of cases, it does not develop in mice. The fish can be taken as another example. Trout is highly sensitive, however, the sensitivity of other Salmonidae is twenty times weaker (and in

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ether fish species still more weaker). Hence, even if the experimental carcinology possessed the factual data on the sensitivity of the hepatic epithelium of the primates to the carcinogenic effect induced by aflatoxins, we could not view the conclusion that these aflatoxins are powerful hepatocarcinogens for man as absolutely correct. Nevertheless, experiments were carried out, the results of which permitted to assume that the carcinogenic response of human and rat organisms to the effect of aflatoxins can be characterised by similar comparative indices (Shank, 1977; Carlberg, 1979). The aflatoxin concentration of 1 ug/kg in diet is known to be characterized by a 10% hepatoma induction frequency in rats. If a rat weights 250 g and dayly consumes 15 g of the diet, the dayly carcinogen (i.e. aflatoxin) intake will constitute 60ng/kg bodyweight. The investigations carried out in Thailand demonstrated that the level of aflatoxin intake reached 50 ng/kg bodyweight in humans. The above level of aflatoxin intake with foodstuffs ensured the 6:10 000 rate of registration of primary liver cancer among the examined population groups. Thus, it is extremely significant to pursue studies aimed at the determination of the existance and correlation pattern between the presence of aflatoxins in human food, possible doses of aflatoxin intake and the incidence of malignant tumors observed in such human population groups.

The studies conducted in a number of developing countries of the tropical zone showed that the content of aflatoxins

in some agricultural products was quite considerable. Most often peanuts and corn, being the main food sources of mass consumption, were contaminated. In Thailand, for example, during some years, up to 49% of all tested peanut samples and up to 35% of corn samples proved to be infected and contaminated. At the same time, the concentration of mycotoxins in the contaminated peanut samples reached 6,5 mg/kg. As peanuts are consumed in large quantities, representing also an ingredient of babyfood for the children suffering from malnutrition (mainly from Kwashiorkor and Marasmus), the fact that considerable amounts of aflatoxin - a powerful hepatocarcinogen - enter the human organism with food, can be considered as proved. It should be noted that the above reports present mean data on the volume of food consumption by the population. The individual amounts of food consumed and, thus, the volumes (doses) of aflatoxin intake can be considerably higher than the average ones. The investigation results related to the aflatoxin carcinogenic effect on experimental animals confirm the risk of human liver cancer occurrence (Linsell, 1982).

The attempts to compare the results of the epidemiological studies of the levels of mycotoxin contamination of food products and raw materials with the data on the morbidity structure, and in this particular case, with the data on the frequency of the malignant neoplasm rates - meet a number of difficulties, including that of determining actual cancer incidence. Thus, it is particularly interesting to have data on the diseases that are, on the one hand, are

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rather frequently and precisely diagnosed and are considered to be pre-cancerous diseases on the other. Liver cirrhosis is one of such precancerous diseases when the problem of the aflatoxin contamination of food and the frequency of the malignant diseases connected with the consumption of mycotoxins with the food products is studied. However, not in all cases liver cancer is preceded by cirrhosis, but all cases of manifested cirrhosis should be considered as cases of obligatory hepatic pre-cancers, the transformation of which into carcinomas is mainly the question of time. As various techniques of life-time morphological and microscopic investigations of the liver, i.e. the use of biopsy for diagnosis became a routine procedure due to the technological advances of the biopsy technology, investigations confirming the development of liver cirrhosis in individuals, consuming aflatoxin-containing food, present a considerable interest. T. Campbell, a prominent researcher of Kwashiorkor (which is caused by protein-deficient food without manifested calory deficiency), has been for a long time investigating the consequences of the changes that occur in the liver of children suffering from Kwashiorkor (possible restitution, development of cirrhosis and cancer, effect of treatment, etc.). The children with manifested clinical symptoms of Kwashiorkor and Marasmus (which is caused by the protein and calory deficient diets) were investigated and the liver biopsy performed. In the course of the treatment of these malnutrition-induced diseases the children received, as a source of protein, peanut flour which contained aflatoxin B_1 in the con-

centration of 0,3 mg/kg. The above investigator established that liver fat infiltration and fibrosis that occured in the presence of Kwashiorkor may be restituted in the course of treatment. In his work on the effect of aflatoxins on hepatic rehabilitation processes Campbell and his colleagues discovered that the consumption of aflatoxin-containing food was accompanied not by the restitution of fatty liver but by its growth into cirrhosis when the level of the histopathological changes depends on the duration of the above intake. No negative clinical or morphological symptoms were reported when the aflatoxin concentration in peanut flour equalled 15 ug/kg.

These results are confirmed by other studies on the correlation between the lesions of the liver and other organs in children and adults and the aflatoxin contamination in food products favours the development of liver cirrhosis in children and adults can be considered as proved. It means that food-contaminating aflatoxins are the substances that increase the potential danger of hepatic cancer in man.

The study of the nature of the correlation between the level of aflatoxin contamination of food and the hepatic cancer incidence in man still confirm the noxious role of mycotoxins.

In one of his reports Wogan collected and analysed the data on the aflatoxin contamination of raw foods and food products, on the consumption rate of such products by various population groups, on the amount of the toxin consumed with the diet, on the incidence of oncological diseases, and

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primary liver cancer. As a result, a direct dependance between the prevalence and the rate of primary liver cancer and the levels of aflatoxin content in food products and daily food intakes, was established. These facts are related to such countries as Uganda, Kenya, Mosambique and Thailand. Such products as raw foods and foodstuffs made of peanuts, corn and manioc were found to be contaminated more often than others. Rice, an important food source for Middle-East and South-East countries, is less liable to aflatoxin contamination, however, even this product, under certain conditions, is "susceptible" to aflatoxin contamination.

While the analysis by Wogan sounds convincing, one more additional factor should be kept in mind: the above mentioned countries represent the regions where primary liver cancer occupies, according to its incidence, a leading place in the general group of malignant neoplasms. It would be, however, incorrect to associate a really high incidence of primary liver cancer only with aflatoxin intake by the population of these regions. Some time ago, a no less strong relationship was established between the high incidence of primary liver cancer registered in the same regions (including the South-East Asia) with the high viral hepatitis frequency especially combined with malnutrition. Pokrovsky A.A., Kravchenko L.V. and Tutelyan V.A. claim that "... one cannot ignore the fact that in the development of hepatomas a certain role is played by other mycotoxins, plant alkaloids, viral infections, helmithiases and malnutrition".

Should we limit ourselves to a more simple question of existing motivation of causal role of aflatoxins (aflatoxin B_1 in particular, which is the main subject of the present discussion) in the development of malignant neoplasms, particularly of primary liver cancer in man, the answer seems to be clear: under certain conditions the damage brought to the liver by aflatoxins plays a considerable and sometimes the major role. If primary hepatic cancer in man can be caused by only one reason - by the epidemic hepatitis virus - then it is as well possible for liver cancer in man to develop as a result of aflatoxin effect. However, is it possible that one and the same disease (human liver cancer) can be caused by both the virus and the toxin?

Aflatoxins are active carcinogenic compounds in relation to liver tissues; their carcinogenic potency to induce, in some cases, the growth of malignant neoplasms located elsewhere, has been also observed. We have reports about aflatoxin-induced carcinomas of the large intestine. At present, a problem of the dependance of the aflatoxin carcinogenic action on the nutrition pattern and, as it is commonly mentioned, on the modifying action of food. This subject will be discussed later. Meanwhile it is necessary to touch upon carcinogenic effects of some mycotoxins inducing malignant extrahepatic tumours.

Some rice-producing and rice-consuming countries faced a problem of the "yellow-colored" rice, the colouring of which was due to its contamination by the microscopic mold fungus Penicillium islandicum. It was established in the

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experiments on rats fed on the "yellow-colored" rice diet that in the course of long-term consumption of this rice hepatomas can develop. Luteoscorin and cycleratin - the products of the metabolism of this mold fungus - are carcinogenic for mice (in contrast to aflatoxin B_1) and can induce various tumours, including reticuloendotheliomas.

Sterygmatocystin which is produced by mycelia Aspergillus versicolor and Aspergillus nodulans is carcinogenic both for mice and rats. When administered orally, this mycotoxin induces pulmonary adenomas and adenocarcinomas in mice and liver tumors in rats. Skin application of this mycotoxin results in the development of papillomas and tumors of various localizations.

Patulin which is produced by the culture Penicillium claviforme contaminates apple juice and cider and is proved to be an active carcinogen inducing sarcomas in experimental animals when administered subcutaneously.

Ochratoxins (A and B) which are produced by Aspergillus ochraceus and also by other Aspergillus strains are not carcinogenic for mice but are carcinogenic for rats, inducing malignant tumours of the connective tissues in the latter. Ochratoxin A (and seldom ochratoxin B) are found to be contaminants of foodstuffs, to possess mutagenic activity, however, there are no data confirming their carcinogenicity for man.

Trichothecenes. Our knowledge involves multiple investigations on various manifestations of these mycotoxins' toxicity for animals and man. Their carcinogenicity related to humans, however, has not yet been documented.

Thus, among active carcinogenic mycotoxins, there are substances that induce malignant growth of various epithelial and mesenchymal tissues in different animal species. Some of them are toxic, and are more likely to be carcinogenic for man.

The discovery of one more group of active carcinogenic substances (oncology deals with hundreds of various carcinogens), naturally, represents a major event. The role of myco- and aflatoxins in the process of malignant neoplasms is determined by the knowledge of these substances' metabolism, by the dependence of their metabolic phenomena and chemical transformations on food metabolism and, finally, it is determined by the level of the knowledge of the carcinogenic mycotoxin effect related to cellular devesion and cellular and tissue differentiation processes.

All investigators admit that toxic and carcinogenic effects of myco- and aflatoxins depend, to a great degree, on the total sum of metabolic transformations caused by the toxin and that occur in the system of microsomal multi-target oxidazes. This system detoxicates and decontaminates various xenobiotics and foreign chemical substances.

It is known that the system of nonspecific microsomal oxidazes that exists or is induced in different tissues of man and animals ensures the metabolism of multiple foreign substances, including chemical carcinogens. Metabolic transformations of chemical carcinogens are associated in this case with various manifestations of their biological activity.

Finally, it is known that various chemical substances

entering the inner medium of man and animals stimulate (induce) the synthesis of nonspecific microsomal oxidazes raising the activity of the above enzymic system in tissues. Many chemical substances that display a variety of biological actions (drugs, pesticides, carcinogens, hormones, and others) can act as such "inductors".

It should be noted and remembered that many investigators have established that the intensification of metabolism of chemical carcinogens by the system of microsomal oxidazes may bring out the following results:

1. More rapid decomposition and detoxication of a carcinogenic substance.

2. The manifestation or the intensification of the toxic action by a carcinogenic substance.

3. The manifestation or the intensification of the blastomogenic activity of a carcinogenic substance.

It has been established (also for mycotoxins) that the capability of chemical substance to induce microsomal oxidazes is not connected with their carcinogenic activity: an active carcinogen and a noncarcinogenic compound may both act as equally powerful inductors for the system of microsomal oxidazes.

The carcinologists do not consider the manifestations of cytotoxic activity of various chemical carcinogens apart from their carcinogenic activity. Such changes of the cellular structure and functions as necroses, membrane injuries, disturbances of cellular division, changes of enzymic spectra - all these factors are now related to major manifestations

of the progressing malignant cellular process. Carcinogenic mycotoxins fully possess these cytotoxic properties.

One must remember that for any, even the most powerful chemical carcinogen (and this is totally true in respect to carcinogenic mycotoxins!), the complete cycle of carcinogenesis, i.e. the formation of malignant tumour, presupposes some proportionality of the detoxication and decontamination processes, on the one hand, and the development processes of the toxic and carcinogenic metabolites, on the other. A rapid discomposition leads to the removal of carcinogenic derivatives from the organism, void of the blastomogenic effect. A considerable increase of toxic products leads to early animal death before the process of carcinogenesis is completed. "The multi-target microsomal oxidazes lack any specificity, thus complicating the forecast of the direction of biological activity related to the developing metabolites. Besides, one cannot eliminate the impact of various side-factors such as species and sex variations, the functional state of animals, diet composition, etc". (B.L. Rubenchik).

The dependence of the final action of carcinogenic aflatoxins on the "balance" of detoxicating and activating (toxicity and carcinogenicity) mycotoxin metabolic processes occurring in the system of nonspecific microsomal oxidazes has been reflected in recent publications in the following way. A.A. Pokrovsky in his book "Metabolic Aspects of the Pharmacology and Toxicology of food" (1979) wrote (page 124): "Despite some controversial results, an impression is being formed that in the process of aflatoxin transformation the

development of new compounds with less pronounced toxic properties is taking place in the organism... Thus, preinjection of phenolbarbital to the experimental animals which induces the activity of microsomal oxidazes with the mixed function considerably diminishes the aflatoxin toxic effect which is displayed in the decreased inhibitory action of aflatoxin B_1 on the RNA synthesis, ... in the prevention of the development of hepatic necrosis and in the reduction of carcinogenic properties of aflatoxin B_1 in cases of chronic intoxications..."

"At the same time, the administration of an inhibitor of microsomal oxidazes SKF 525 A contributed to the development of manifested morphological hepatic transformations under aflatoxin effect... In young animals... in cases of radical reduction of the protein content in the diet and in cases of A vitamin deficiency an increase in the sensitivity to the toxic action of aflatoxin (against the background of decreased activity of microsomal enzymic systems) was observed, however, alongside with it, in some cases the frequency of hepatoma development was reduced...

Recently, there has appeared more alternative data pointing at possible formation, at least in some cases, of even more toxic metabolites than aflatoxin B_1".

Thus, the variability of the system nonspecific microsomal oxidazes predetermines, to a great degree, the biological (and carcinogenic) mycotoxin effect.

However, the question of the active carcinogenic form of aflatoxins that appear in the process of the toxin metabolism, deserves considerable attention.

Here, the following should be noted.

In the specialized literature it is accepted to differentiate chemical carcinogens into "direct" or "genuine" carcinogens that can induce malignant growth without any additional transformations, and "secondary" or "procarcinogens", which are transformed into blastomogenic metabolites resulting in blastomogeneeis. Many new carcinogenic metabolites are being discovered, hence, the number of "direct" carcinogens is reduced while the number of "secondary" carcinogens increases. And finally, the analysis of the metabolism of initial forms of "secondary" carcinogens (i.e. the precarcinogens) led to the discovery of intermediate (proximal) and terminal carcinogens. It was found that intermediate carcinogens possess in the first respect a more manifested blasomogenic activity (compared with their initial chemical precursors), and, secondly, they display a less pronounced tropism of action. "Terminal" carcinogens possess these properties even to a greater degree.

It is the latter, i.e. "terminal" metabolites of chemical carcinogens that display the existence of a reactive electrophilic centre - the atom with a missing electrone. This electrophilic centre is involved in the reaction of carcinogenic lesion with negatively charged molecule particles of nucleic acids or proteins.

Now let us go back and consider the problem of the active carcinogenic form of aflatoxins emerging in the process of their metabolism.

Some researchers think that, likewise other carcinogens,

the active forms of aflatoxins B_1, G_1 and M_1 can represent their epoxides. It is believed that the double bond of the terminal furan ring of the molecule of aflatoxins B_1, G_1 and M_1 which are most toxic in the aflatoxin group, can epoxide. While the molecules of aflatoxins B_2 and G_2 possess no such double bond, thus, according to the theory, their biological activity is much lower.

Animal investigations and experiments on human and animal cells showed that aflatoxins, like other hepatocarcinogens, inhibit the synthesis of DNA, RNA and protein. It was found that the active electrophilic metabolite of aflatoxin binds nucleic acids and polynucleotides.

It was established in the laberatory headed by A.A. Pokrovsky that aflatoxins impair lysosome membranes; moreover, this membranotropic action was observed only in rats (i.e. animals sensitive to aflatoxin action) and was not found in resistant animals (mice, sheep). In this connection, A.A. Pokrovsky believes that aflatoxin carcinogenicity is related to two effects of their toxic action: 1) with the impairment of lysosome membranes accompanied by the release of hydrolazes favouring the toxin penetration into the nucleus; and 2) with the interaction of the toxin active metabolite with a DNA molecule.

It has been mentioned before that the presence of aflatoxin B_1 in the diet leads to the development of malignant hepatomas in 100% of experimental animals. In case of long-term administration of the aflatoxin and the consequent long-term latent period, the formation of renal carcinomas was ob-

served in rats. The tests were performed as follows: aflatoxin B_1 was added into the diet which was fed to the animals during 147 days. Then the animals were put back to their ordinary feeding and remained under observation till their natural deaths. Renal carcinomas were reported in 57% of cases in the rat group fed on the aflatoxin diet in the amount of 1.0 mg/kg; in 28% in the group with the aflatoxin amount of 0.5 mg/kg, and in 2% with 0.25 mg/kg of aflatoxin.

The morphogenesis of hepatomas caused by the aflatoxin is of the same character as in cases when tumours are induced by ethionine (which can also cause only hepatocellular carcinomas): the formation of proliferation foci of hepatic epithelium: hyperplasia nodes - adenomas - hepatomas.

It should be noted that aflatoxin B_1 is characterized by mutagenic properties causing all manifestations of chromosomal abberations in plant and animal cells, as well as gene mutations in microbic test systems. It is significant that the mutagenous effect of this toxin is not manifested in mice (resistant to toxic and carcinogenic actions of aflatoxin B_1).

Of considerable significance is the question of the modifying effect of nutrition on mycotoxin-induced carcinogenesis. The following facts have been revealed.

The lipotropic-deficient diet of experimental animals inhances the carcinogenic effect of aflatoxins. The addition of choline and methionine to the diet inhibited, however, did not prevent the induction of hepatomas and the very process

of carcinogenesis.

The protein deficiency (5% of casein) contributed to the intensification of intoxication symptoms. The animal death limited the period of tumours growth. Under moderate protein deficiency (9% of casein) the number of hepatomas increases compared with the group of animals receiving 20% of protein.

The data have been collected indicating that under the conditions of protein-deficient food with a deficient content of some essential aminoacids, no hepatomas developed, but in rats fed in aflatoxins, carcinomas of esophagus and the pancreas were detected.

Thus, the nutritional pattern considerably influences metabolic processes and carcinogenic effects of aflatoxins.

In conclusion the following should be emphasized. Biochemical and morphological processes of carcinogenesis induced by mycotoxins have, according to the indications meaningful for tumour development, a considerable similiarity with carcinogenesis caused by other chemical carcinogens. Among mycotoxins there are some very potent carcinogens. The evaluation of the carcinogenic activity of these toxins appears to be related, to a certain degree, with two specific mycotoxin properties. The first consists in the damaging mycotoxin action on cellular membranes. The second represents a dependence of the carcinogenic effect on that of alimentary factors. Thus, the model of mycotoxin carcinogenesis presents an exeptionally high interest for the investigators engaged in the field of cancer research.

Addendum

Table 1. Carcinogenic-active mycotoxins identified by the IARC Group of Experts

No.	Toxin	Fungus producer	Contaminated products	Animal species. Mode of administration		Localisation and type of tumour	Carcinogenicity for animals
1	2	3	4	5	6	7	8
1.	Aflatoxin B_1	Aspergillus flavus	peanuts, beans, cereals (less frequently rice)	mice	per os	0	-
				rats	per os	hepatocellular cancer (seldom intestinal and antral tumours)	+
				fish	per os	hepatomas	+
				ducklings	per os	- " -	+
				primates	per os	- " -	+
				mice	p. perit.	lung adenomas	+
				rats	p. perit.	hepatomas	+
2.	Aflatoxin B_2	Aspergillus flavus	peanuts, beans, cereals (less frequently than with aflatoxin B_1)	rats	per os	hepatomas	?
				trout	per os	- " -	+

Table 1. (Cont.)

1	2	3	4	5	6	7	8
3.	Aflatoxin G_1	Aspergillus flavus	peanuts, beans, cereals (less frequently than with aflatoxin B_1)	rats	per os	renal tumours, hepatomas	+
				trout	per os	hepatomas	+
4.	Luteoscorin	Penicillium islandicum	cereals, especially rice	mice	per os	hepatomas	+
5.	Cyclochloratin	Penicillium islandicum	- " -	mice	per os	hepatomas and reticuloendotheliomas	+
6.	Griseofulvin	Penicillium griseofulvum urticae, Patulinum and others	soya bean paste	mice	per os sub.cut.	hepatomas	+
7.	Ochratoxin A	Aspergil. ochraceus and other Aspergill. and Penicill.	cereals, beans, peanuts, malt, beer	mice	sub.cut.	0	?
				rats	sub.cut.	fibrosarcomas	?

Table 1. (Cont.)

1	2	3	4	5	6	7	8
8.	Patulin	Penic. claviforme expancum and others	apple juice, cider	rats	sub.cut.	sarcomas	?
9.	Penicillin acid	Penicillium (various species)	cereals, beans	mice rats	sub.cut. sub.cut.	sarcomas	?
10.	Sterigmatocystin	Aspergillus versicolor, nodulans	solami sausages, corn, coffee	mice rats	per os per os sub.cut. per.cut. (appl.)	lung adenomas and carcinomas hepatomas tumours of various localisations skin papillomas hepatomas	+ +

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