

ASSESSMENT OF ESTIMATED RISK
RESULTING FROM
AFLOATOXINS IN CONSUMER PEANUT PRODUCTS
AND OTHER FOOD COMMODITIES

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SUMMARY

Although direct proof that aflatoxins (B₁, B₂, G₁, G₂) induce cancer in humans does not exist, laboratory tests have demonstrated that they are animal carcinogens. Further, epidemiology studies in Thailand and parts of Africa show a significant relationship between liver cancer incidence and estimated levels of aflatoxin intake.

Aflatoxins cannot be completely eliminated from food products without eliminating the products themselves. FDA has been enforcing a limit of 20 parts per billion (ppb) for aflatoxins in certain foods and is considering reducing that limit to 15 ppb for peanuts and peanut products (39 FR 42748).

Unfortunately, the direct risks, if any, to humans from ingestion of aflatoxins cannot be measured. Therefore, risk assessments must rely on mathematical treatment of animal toxicology and epidemiology studies. Such risk assessments have been made by FDA and are described herein.

Aflatoxins can occur in a variety of grains and nuts and can also occur in the meat, milk, and eggs of food animals that have consumed aflatoxin-containing feeds. Corn products and peanut products only have been considered in the risk calculations since inclusion of other products, because of contamination levels and/or frequency of contamination or consumption does not significantly affect the numerical results. Emphasis has been placed on corn products in the Southeastern United States because both consumption and aflatoxin contamination levels are relatively high in that region.

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Utilizing FDA and USDA aflatoxin survey and food consumption data, it is estimated that aflatoxin intake ranges from an average of 2.7 to a maximum of 9.0 nanograms/kilogram of body weight/day (0.1 to 0.3 parts per billion in the diet) in the Southeast.

An extensive body of data exists on aflatoxin toxicology in ~~laboratory animals~~. Because it would be impractical to make risk calculations for each such study, five studies, involving long-term feeding of aflatoxins to three species of rats, were selected. (Rats in general, and male rats of the Fisher strain in particular, are considered the most aflatoxin-susceptible mammals.) Using the mathematical procedure of Mantel and Bryan, estimates of lifetime liver cancer incidence rates were derived for each study, and for the five studies combined. These estimates range from 30 to 1400 per 100,000 for the individual rat studies and from 240 to 1100 per 100,000 for their combination. By way of comparison, risk estimates derived from studies on rats and other species combined by Cornfield and co-workers yield a range from 17 to 126 per 100,000.

The actual lifetime liver cancer incidence rate from all causes in the U.S. is approximately 161 per 100,000. Actual incidence rates in Georgia and Alabama are approximately 103 and 100 per 100,000 respectively. (Rates for other Southeastern states are not readily available.)

The fact that the risk estimates for rats in general exceed the human incidence rate for liver cancer from all causes can be attributed, in part, to the conservative mathematical procedures employed. In

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addition, available in vitro data would indicate that humans are biologically closer to relatively resistant animals such as mice and monkeys than to aflatoxin-susceptible rats.

Epidemiology studies conducted in Thailand and several parts of Africa show a positive correlation between actual liver cancer incidence and estimated intake of aflatoxins. Utilizing the relationship derived by Peers and Linsell, risk estimates were calculated to range from 20.2 to 67.0 per 100,000 for estimated average and maximum aflatoxin intakes. How applicable such epidemiological studies are to the U.S. is not known, particularly since the liver cancer incidence rates in these areas outside the U.S. may be greatly influenced by the presence of pyrrolizidine alkaloids in herbal medicines and the existence of hepatitis-B virus.

Risk estimates calculated from the epidemiology data for peanut products only yield a range of 1.1 to 2.7 per 100,000. Assuming that a proportional reduction in aflatoxin levels would result from the proposed regulatory enforcement limit of 15 ppb yields a projected range of 0.8 to 2.1 per 100,000. For the lowest enforcement limit currently possible, 5 ppb, the theoretical range would be 0.3 to 0.7 per 100,000. Although the ranges are broader, the animal data yield a similar comparison between a limit of 15 ppb and that of 5 ppb.

Neither the estimated incidence rates calculated from the animal data nor those from the epidemiology studies can be construed as representing the actual human risk from aflatoxins. It is reassuring,

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however, that the two approaches yield similar results, at least when inter-species differences are taken into account. Assuming that these approaches at least provide conservative indications of potential human risk, there appears to be little, if any, gain in public health protection associated with a tolerance for aflatoxins in peanut products at 10 ppb or 5 ppb as opposed to the 15 ppb level being considered. Again assuming that these approaches have some validity, it appears prudent to continue efforts to control the largely intra-state problem with aflatoxins in corn in the Southeast--notwithstanding the apparently lower actual incidence of liver cancer in the Southeast.

The several other reasons why a 15 ppb tolerance for aflatoxins in consumer peanut products is deemed appropriate were described in the preamble to the proposal to establish the tolerance.

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INTRODUCTION

The Food and Drug Administration (FDA) is considering a regulation that establishes a tolerance for aflatoxins in shelled peanuts and peanut products used as human food. The regulation would set a 15 parts per billion (ppb) tolerance for total aflatoxins ($B_1 + B_2 + G_1 + G_2$) in these products.

Aflatoxins are mold-produced toxins which are unavoidable contaminants in peanuts and a number of other food commodities (1). Although the human health effects of chronic exposure to aflatoxins are not known with certainty, there is evidence which associates chronic dietary exposure to aflatoxins with the induction of primary liver cancer. In particular, several studies have indicted aflatoxins as animal carcinogens (2).

At present, it is not possible to determine a level of dietary exposure to carcinogenic substances that would not lead to a finite risk of human cancer. Therefore, assurance of absolute safety for the consumer (i.e., no risk of cancer) is achievable only through complete elimination of carcinogenic substances from the diet and from other sources. However, unlike chemicals intentionally added to food, unavoidable food contaminants cannot be prohibited from the diet, unless the food susceptible to contamination is itself prohibited.

This approach to the assurance of absolute safety for food unavoidably contaminated with aflatoxin would mean the complete elimination of those food commodities that have been shown to be susceptible to such contamination. These food commodities include corn, peanuts, sorghum, rice, wheat, soybeans, walnuts, almonds, pecans, pistachio nuts, Brazil nuts, figs, and the edible

tissue (meat, eggs, and milk) from food-producing animals that consume animal feed containing these compounds (3,4).

Because not all lots of these foods are expected to contain measurable aflatoxins, an alternative approach to indiscriminately eliminating from the diet both contaminated and non-contaminated food is to prevent from entering consumer channels only those lots demonstrated to contain aflatoxin.

In the case of consumer peanut products, aflatoxins at or above a level of 5 parts per billion (ppb) can be measured with the degree of certainty required of FDA to initiate regulatory action (e.g., seizure) to prevent the marketing of aflatoxin-contaminated peanuts. In short, the goal of attaining a "zero" tolerance for aflatoxin would translate to an enforcement level of 5 ppb, i.e., the lowest level at which it can be determined with certainty whether aflatoxin is or is not present in peanuts. (It should be noted that aflatoxins at levels less than 5 ppb can be detected in peanuts, but the validity of measurements at such levels is questionable.)

While a level of 5 ppb may represent the lowest enforceable tolerance consistent with FDA's consumer protection objectives of minimizing dietary exposures to aflatoxins, such a tolerance would be beyond the capability of manufacturers to meet consistently. This is the case because of the high variability of aflatoxin levels within and among peanut lots. Such variability requires that quality control limits in manufacturing be set much lower than the regulatory tolerance (5). For example, consistent production of lots conforming to the proposed tolerance of 15 ppb would require quality control limits on the order of 5-7 ppb. Lower tolerances would require proportionately lower quality control limits. A tolerance of 5 ppb would thus

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require a quality control limit below the level of reliable detection and would result in the inadvertent release of illegal lots into commercial channels, there to be seized by FDA.

In brief, if peanut products are not to be entirely prohibited, consumer exposure to aflatoxins from these products can only be kept below detectable levels (i.e., 5 ppb) by seizure (and a significant loss of product). For a higher tolerance (e.g., 15 or 10 ppb), the emphasis would be on manufacturing quality control (and there would be less loss of product).

Because of the foregoing characteristics of the control situation, information is needed to assess the human risks associated with low levels of aflatoxin exposure. Unfortunately, such information is not readily available. However, evaluation of that information which is available from toxicology and epidemiology studies does help to put the risk question in perspective. In the following, risk estimates are derived from animal tests and from epidemiology studies. Such estimates cannot be construed as representing actual human risk but they do provide an indication of the relative potential toxicity of aflatoxins.

INFORMATION NEEDED FOR RISK ASSESSMENT

Existing data indicate that the most likely potential effect from chronic aflatoxin exposure is primary liver cancer (1,2). In all risk estimates to follow, it is this disease that is being considered.

An estimate of the risk of primary liver cancer in humans due to exposure to dietary aflatoxins requires two types of information. First, some measure of the toxicity of aflatoxin to humans must be available. For purposes of

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this assessment, the most relevant toxicity data would be those relating to long-term, low-level aflatoxin exposure to primary liver cancer in the exposed group. Ideally, what is sought is a dose-response curve expressing the relationship between the level of aflatoxin exposure (the dose) and the incidence of liver cancer (the response) in the exposed group.

The most relevant and least suspect of such information would be that obtained by direct experimentation in human beings. Clearly no such data are available nor, for ethical reasons, could they ever be developed. Therefore, reliance must be placed on data resulting from: 1) epidemiological studies in groups of humans known to have been inadvertently exposed to aflatoxins; or 2) direct experimentation in laboratory animals. Epidemiological studies, which should provide the most relevant information obtainable, nonetheless have several disadvantages, perhaps the most important of which are their inherent limitations in establishing clear causal relationships and their relative insensitivity in detecting such relationships. Studies in experimental animals are usually more sensitive than epidemiological studies and, when properly conducted, are capable of establishing direct causation and dose-response relationships of relatively high certainty. But they have been criticized on the grounds of being irrelevant to humans. It must also be kept in mind that epidemiological and animal data obtained from relatively small, homogenous population groups requires, for estimation of risks in an entire population, extrapolation to very large, heterogeneous groups of humans. It is not known how to estimate the uncertainty associated with extrapolations of these types.

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In addition to toxicity information, risk assessment depends on data concerning the level and duration of human exposure to the toxic material. For purposes of this assessment, the relevant data are the food commodities in which aflatoxins occur, the levels of aflatoxins in those foods, the frequency and amounts of human consumption of those foods, and the length of time of exposure. As with the toxicity information, the human exposure factor in the risk assessment equation is also subject to much uncertainty.

DIETARY EXPOSURE TO AFLATOXINS

a. Occurrence of Aflatoxins in Food: The food classes that contribute most significantly to dietary exposure to aflatoxins in the United States are dry milled corn products (e.g., corn meal and grits) and peanuts and peanut products (3). Exposure to aflatoxins through contaminated corn occurs mainly in the southeastern states (i.e., North Carolina, South Carolina, Georgia, Alabama, Florida, Mississippi, and Louisiana), where the contamination of corn is most severe. In this area corn is a dietary staple and the corn consumed is primarily of local origin. On the basis of FDA and USDA survey data, it is estimated that the average level of total aflatoxins in dry milled corn products has been in the range of 5-10 ppb (3,6,7). Corn produced and consumed in other regions of the nation has a substantially lower aflatoxin content. Therefore, the United States population groups that appear to be at highest risk, those of the southeastern states, have been selected for emphasis in this risk assessment. To be conservative, the upper level of 10 ppb is used in the risk calculations.

Peanuts, while grown in the Southern states, are processed and consumed throughout the country. Data from surveys conducted by FDA indicate an estimated average level of 2 ppb total aflatoxins in consumer peanut products (3,6,7). This estimated level is equally applicable to population groups on a national or regional basis.

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As previously mentioned, aflatoxins may also occur in other food commodities consumed in the United States. However, survey and experimental data indicate that either the levels and/or incidence of aflatoxin in these foods and/or their consumption patterns are not comparable to those found in peanuts and corn (3,6,7). Calculations used in the estimates of total risk would not be significantly affected by ignoring these other food items.

The relevant data on the aflatoxin occurrence in food is presented in Table I.

TABLE I: Major Food Classes With Aflatoxins ($B_1 + B_2 + G_1 + G_2$)

Food Class	Estimated Average Level (total aflatoxins, ppb)
Peanuts and Peanut Products	2
Corn Products	5-10 *

* Average is for Southeastern States; average in all other areas is lower (see text).

b. Consumption of Aflatoxin - Containing Food Products: A survey conducted by the U.S. Department of Agriculture (USDA) in 1965 provides the best available data for estimating human consumption of the significant food sources of aflatoxins (8). The USDA survey data were collected through personal interviews which required the respondent to recall all foods and the amounts actually consumed during the 24-hour period prior to the interview. The data collected, which covered the entire United States, are available for four major regions--Northeast, North Central, West, and South.

For purposes of this risk assessment, the data collected for the Southern region were used. This survey region included the states of Alabama, Florida, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Arkansas, Kentucky, Delaware, District of Columbia, Maryland, Oklahoma, Texas, Virginia, and West Virginia. Although it would have been more appropriate to base estimates of intake on the southeastern states alone (i.e., the first seven states listed), since dry milled corn products which may contain aflatoxins are mainly produced and consumed in these states, the food intake estimates used in the risk calculations assume that dietary patterns of the South and Southeast are identical.

Food intake estimates were used for the consumer peanut products and dry milled corn products listed in Table II.

TABLE II: Food Items From USDA Survey Used To Estimate Intake Of
Aflatoxin-Susceptible Food (8).

Consumer Peanut Products

peanuts, shelled and in-shell	peanut butter & jelly sandwich
peanut butter	peanut butter & banana sandwich
peanut butter sandwich	peanut butter & jelly

Dry Milled Corn Products

corn bread & muffins	cornmeal pancakes
corn pone	corn grits, hominy grits
spoonbread	cornmeal, cornmeal mush
johnnycake	grits with fat
hush puppies	fried cornmeal mush

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The estimated average levels of aflatoxins in consumer peanut products and dry milled corn products (Table I) are derived from surveys of these food items as marketed as opposed to food items prepared for consumption (i.e., as eaten). Therefore, conversion factors were applied, where appropriate, to the amount of intake of food items listed in Table II to obtain the amount of intake expressed in terms of the food items listed in Table I.

Calculation of the average and maximum daily intakes of foods susceptible to aflatoxin contamination also requires knowledge of the frequency at which these foods are consumed. Direct knowledge of the frequency of consumption of these foods is not available. To estimate daily consumption, it was necessary to make use of the information that the total population in the South surveyed by USDA consisted of 6,268 persons, 560 of whom had eaten peanut products and 1,580 of whom had eaten corn products during the 24-hour period preceding the questioning. Since it would be expected that these individuals would not consume these foods every day, the ratio of "eaters" for one day versus "non-eaters" for one day was used to establish the estimated frequency at which these foods were eaten. This ratio, or frequency factor, was applied to both the average amount and to the amount consumed by the 90th percentile of the "eaters" surveyed to derive an estimate of average and maximum daily intakes. These estimates are presented in Table III.

TABLE III: Estimated Consumption Rates For The Southeastern United States Of Food Products Which May Contain Aflatoxins.

	<u>Peanut Products</u>	<u>Corn Products</u>
One day average intake (grams)	45	53
One day maximum (90th percentile) intake (grams)	116	186
Factor for frequency of consumption	.090	.252
Estimated average daily intake (grams)	4	14
Estimated maximum daily intake (grams)	10	47

c. Human Exposure to Aflatoxins: The estimates of consumption contained in Table III can be combined with the levels of aflatoxin contamination (Table I) to estimate average and maximum human exposure to aflatoxins in the southeastern part of the country (the exposure in all other regions being lower). The results of these calculations are presented in Table IV. Also shown are the estimated average and maximum human intakes of dietary aflatoxin expressed in ng/kg body weight/day and in parts per billion (ppb) in the diet.

TABLE IV: Estimated Average and Maximum Daily Aflatoxin Intake In The Southeastern U.S.

FOOD CLASS	<u>Average</u>			<u>Maximum</u>		
	<u>ng</u> ^{1/}	<u>ng/kg</u> ^{2/}	<u>ppb</u> ^{3/}	<u>ng</u> ^{1/}	<u>ng/kg</u> ^{2/}	<u>ppb</u> ^{3/}
Peanuts and Peanut Products	8	0.15	0.005	20	0.37	0.013
Corn Products	140	2.58	0.093	470	8.66	0.313
TOTAL	148	2.73	0.098	490	9.03	0.326

^{1/} ng = nanograms (1×10^{-9} grams)

^{2/} ng/kg body weight; average body weight of 54.3 kg

^{3/} ppb in diet; average daily food intake of 1500 g

RISK ASSESSMENT

a. Animal Toxicity Data: The toxic effects of aflatoxin have been examined in several studies in a variety of species and strains of experimental animals. These include several strains of rats as well as mice, marmosets, tree shrews, trout, ducks, rhesus monkeys, and hamsters (2). The literature is much too extensive to cover exhaustively in this report. Therefore, selected studies are employed in the following to illustrate the range of results obtained in animal studies. Generally, the rat, and in particular the male Fisher strain rat, is considered the mammalian species that is most sensitive to aflatoxin carcinogenesis (2). For this assessment, five studies involving three strains of rats were examined and the statistical procedure developed by Mantel and Bryan (9) as modified (10) was applied to the experimental results. This statistical procedure is one of several available which allow the estimation of carcinogenic risks associated with dose levels of the carcinogen below those necessary to yield a positive carcinogenic response in the animal experimentation. In the present example, the levels of interest are the average and maximum intakes, 0.1 and 0.3 ppb aflatoxins, respectively (see Table IV). No experiments have been conducted in rats at these low dose levels, so no direct measure of risk can be made; but, as noted, the Mantel-Bryan procedure can be applied to the available animal data to estimate the risks associated with the 0.1 and 0.3 ppb dose levels. It must be kept in mind that the Mantel-Bryan procedure estimates animal, not human, risks. The relative sensitivities of humans and, in the present case, rats, remains to be considered. The results of the risk assessment in rats are presented in Table V.

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As can be seen from Table V, the estimated lifetime liver cancer incidence rates vary widely among the rat studies, ranging from a low of 30 to a high of 1400 per 100,000. Another indication of the inherent variability in these experiments is provided by the upper 99% confidence limits of risk shown in parentheses in Table V.

TABLE V: Estimated Lifetime Cancer Risks In Laboratory Animals (Rats)--
Incidence Rate Per 100,000^{1/}

DATA SOURCE (Reference No.)	AFLATOXIN INTAKE (0.1 ppb)	(0.3 ppb)
(11)	2/(60) ^{3/}	2/(320) ^{3/}
(12)	30(220)	160(990)
(13)	70(600)	360(2300)
(14)	140(620)	650(2400)
(15)	320(1400)	1400(4600)
COMBINED RAT STUDIES	240(470)	1100(1900)
COMBINED ANIMAL STUDIES ^{4/}	17(--)	126(--)

^{1/} Incidence rates are based on the procedure of Mantel and Bryan (9), as modified by Mantel, et al. (10).

^{2/} Cannot be estimated.

^{3/} Numbers in parentheses are upper 99% confidence limits.

^{4/} Includes rats, rainbow trout, ducks, and tree shrews. See text.
Risks are graphically estimated.

The upper 99% confidence limits on the lifetime risks derived from the studies in Table V are not only conservative risk estimates (i.e., they represent a "worst case" estimate), but also are useful for comparing the several studies since the confidence limits take into account differences in sample size and other variables in experimental design.

Although the results of these five rat studies are too variable to justify statistically their pooling, they have been combined in Table V to indicate an overall level of response in rat studies involving different strains.

Another approach to aflatoxin risk assessment based on animal studies is that taken by Cornfield, et al. (16). Combining data from experiments on the rainbow trout, duck, tree shrew, and six different studies on five different strains of rats, these authors fitted various mathematical models. A probit model with a slope of 1.2 probits per $\log_{10}$ dose appeared to give the best fit. Estimates from graphs in this paper yield lifetime incidence rates of approximately 17 and 126 per 100,000 for doses of 0.1 and 0.3 ppb, respectively.

As shown in Table IV, the average and maximum dietary intakes of aflatoxin contributed by peanuts are approximately 0.005 and 0.01 ppb, respectively. For the combined rat studies, the risk estimates for these aflatoxin levels are 2 and 7 per 100,000, respectively. Utilizing the Cornfield approach yields risk estimates on the order of less than 0.1 per 100,000 (graphically estimated) for the 0.005 and 0.01 ppb levels.

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To assess the reasonableness of these animal derived risk estimates, it is of interest to compare them to the overall human liver cancer incidence rates in the United States. The total crude incidence per year of primary liver cancer in the total United States population, estimated in 1969, was $2.2/10^5$ (17). For purposes of comparison with the lifetime animal risk data, it is necessary to break down the above crude yearly incidence rate in terms of age-specific rates, to multiply each age-specific rate by a factor which reflects the proportion of the total liver cancer rate contributed by members of that age group, and then to multiply each such age-specific rate by the expected human lifespan of 70 years. Recombining the age-specific rates yields a calculated lifetime risk for liver cancer occurrence of 161 for every 100,000 in the total U.S. population. Primary liver cancer lifetime incidence rates in Alabama and Georgia, estimated in the same way, are $100/10^5$ and $103/10^5$, respectively (18). The rates for these two states, which are the only ones readily available for the southeastern states, are most appropriate for comparison with the risks estimated from the animal data since they represent the region with the highest anticipated exposure to aflatoxins.

The risks calculated from the rat data in Table V not only differ greatly among themselves, demonstrating an intraspecies difference in susceptibility, but, at the 0.3 ppb dose level, individually exceed the lifetime risks of primary liver cancer in the human population of the United States from all causes. Possible explanations for these differences are: 1) the level of human exposure to aflatoxin has been over-estimated; 2) the Mantel-Bryan extrapolation procedure is overly conservative in this case; and/or 3) rats may not be an appropriate model for predicting aflatoxin-induced

primary liver cancer in humans. While data to test the validity of the first or second explanation are not available, the third receives some corroboration from studies showing differences in aflatoxin metabolism among various animal species, most relevant of which are the differences between rats and humans observed in vitro. Available in vitro data indicate that the ability of an animal species to metabolize aflatoxin B₁ to a metabolite called aflatoxicol (AFL) is related to the sensitivity of the species to acute aflatoxicosis, and that the ratio of reductive and oxidative activities, measured as the ratio of AFL concentration to that of an oxidized metabolite known as Q₁, is an index of species susceptibility to the carcinogenic effects of B₁. Although in vitro data for humans are extremely limited, the data available indicate that, with respect to these modes of metabolic behavior, humans are closer to relatively resistant species such as mice and monkeys than they are to the highly susceptible rat strains (19).

b. Epidemiology Data: Data reflecting actual consumption of aflatoxins over defined periods of time by particular individuals who develop liver cancer are not available. The data most closely representing that situation are those derived from studies in Thailand (20), Kenya (21), Mozambique (22), and Swaziland (23). For two or more districts in each of these countries, average aflatoxin content in samples of meals actually consumed were determined. These estimates of average aflatoxin content were then correlated with official annual liver cancer mortality statistics. As previously stated, there are limitations to these epidemiology data, not the least of which is their inherent inability to establish direct cause-effect relationships. For example, any comparison based on these epidemiological data

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rests on the assumption that sample meals are representative, that current contamination levels are indicative of past experience (i.e., 10-20 years ago), and that there is no significant exposure to other possible causes of liver cancer.

With respect to other possible causes, there is evidence that pyrrolizidine alkaloids consumed in herbal medicines and hepatitis-B virus may play a role in the etiology of primary liver cancer in some of the areas studies (24,25). Thus, the appropriateness of applying the human epidemiology data derived from these studies to low-incidence western countries is questionable. Several other interfering factors, well-described by van Rensburg (24), further cloud the epidemiological data. The calculations made below should be considered against this background of uncertainty.

The results of the various epidemiology studies have been standardized by van Rensburg (24) and these data are presented in Table VI. There is a highly significant positive correlation between cancer rate and estimated level of aflatoxin B₁ intake in the geographical areas studied, and a linear relationship between log aflatoxin B₁ level and cancer incidence, expressed as follows:

$$y = 6.449 \log_{10} x - 2.4115$$

where y = total cancer rate/ 10^5 /year and x = aflatoxin concentration in ng/kg/body weight/day.

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TABLE VI: Summarized Results of Epidemiology Studies Measuring Primary Liver Cancer Rate and Aflatoxin Intake (ng/kg body weight/day).
(From Reference 24.)

Locality	Liver Cancer Rate (10 ⁵ /year)	Estimated Aflatoxin Intake (ng/kg body weight/day)
Kenya - High Altitude	0.7	3.5
Thailand - Songkhla	2.0	5.0
Swaziland - Highveld	2.2	5.1
Kenya - Middle Altitude	2.9	5.8
Swaziland - Middleveld	4.0	8.9
Kenya - Low Altitude	4.2	10.0
Thailand - Ratburi	6.0	45.0
Swaziland - Lowveld	9.7	43.1
Mozambique - Inhambane	13.0	222.4

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Using the estimated average and maximum chronic exposures for dietary levels of aflatoxins in the southeastern states (2.7 and 9.0 ng/kg body weight/day, respectively, Table IV) and the log relation between dietary aflatoxin and cancer incidence derived from the epidemiological studies, the calculated range in the expected crude cancer incidence/year is 0.37 to 3.74 per 100,000. The actual crude rates/ 10^5 /year in Alabama and Georgia are 0.97 and 1.18, respectively (18).

It should be noted that the above calculations involve a significant assumption that quite possibly is not the case. They assume that the background liver cancer rate (i.e., that rate due to unknown factor(s) other than aflatoxin present in the areas of the epidemiological studies) is equal to that of the United States. Of course, there is also the implicit assumption that aflatoxin contributes to the rate of liver cancer in this country; there is no evidence that this is true. And certainly there are other substances in the environment, including the workplace, that are known to be hepatotoxic and could contribute to this disease rate.

In an attempt to reduce the effects of this possible error, a different type of risk estimate has been made. Specifically, a linear, non-logarithmic relationship, derived from the human epidemiological data tabulated by Peers and Linsell (26), allows estimation of the human cancer rate related to dietary aflatoxins (or to other interfering factors, since these epidemiologic studies cannot conclusively show that the increased rate of liver cancer above background is due only to dietary aflatoxin). The relationship is:

$$y = .106 x + 2.2,$$

where y and x have the same meaning as above and 2.2 is the background cancer incidence/ 10^5 /year when $x = 0$.

ESTIMATES OF RISKS AT ALTERNATIVE TOLERANCES

Using the last derived relationship, theoretical risk estimates have been made for various aflatoxin levels that might result from alternative tolerances. These are shown in Table VII and are based on the assumption that the legal maximum level of aflatoxins in peanut products is directly proportional to the average level of aflatoxins actually found in these products. For example, the current FDA action level of 20 ppb leads to survey estimates of average levels of 2 ppb in peanuts and peanuts products and 10 ppb in dry milled corn products. This information is based on data collected while the 20 ppb action level was in effect for all food commodities. If one assumes a direct proportional relationship, a reduction of the 20 ppb level to 15 ppb for peanuts and peanut products could produce an average level of 1.5 ppb aflatoxins in this type of food. Similarly, a reduction of the tolerance to 10 ppb and 5 ppb could produce average levels of 1.0 ppb and 0.5 ppb, respectively. Since, for purposes of this assessment, the legal limit for corn is not under consideration, the estimated average level of aflatoxins in this food is held constant.

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TABLE VII: Estimated Lifetime Cancer Rates Based on Epidemiology Studies - Incidence Rates Per 100,000 $\frac{1}{4}$

PEANUTS $\frac{2}{4}$			CORN $\frac{3}{4}$			TOTAL	
Aflatoxin Level	Risks Resulting From Daily Intake $\frac{4}{4}$		Aflatoxin Level	Risks Resulting From Daily Intake $\frac{4}{4}$		Risks Resulting From Daily Intake $\frac{4}{4}$	
(ppb)	<u>Average</u>	<u>Maximum</u>	(ppb)	<u>Average</u>	<u>Maximum</u>	<u>Average</u>	<u>Maximum</u>
2	1.1	2.7	10	19.1	64.3	20.2	67.0
1.5	0.8	2.1	10	19.1	64.3	19.9	66.4
1.0	0.5	1.3	10	19.1	64.3	19.6	65.6
0.5	0.3	0.7	10	19.1	64.3	19.4	65.0

1/ Based on Peers and Linsell (26). See text.

2/ Aflatoxin levels are those which might be expected in peanuts and peanut products if the tolerance were reduced from the current 20 ppb to 15, 10, and 5 ppb, respectively.

3/ Aflatoxin levels in corn products assumed to be an average of 10 ppb.

4/ Incidence rate per 100,000 population.

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As shown in Table VII, the theoretical cancer rates over a lifetime of exposure (70 years) are estimated for the Southeast to range from 20.2 to $67.0/10^5$ at the current 20 ppb action level; 19.9 to $66.4/10^5$ at a 15 ppb tolerance, 19.6 to $65.6/10^5$ at a 10 ppb tolerance and 19.4 to $65.0/10^5$ at a 5 ppb tolerance.

Thus, based on the epidemiological data (26), assessment of the estimated risk of human exposure to varying levels of aflatoxins in peanuts and peanut products shows relatively no significant gain in the protection of the public health (i.e., reduction in liver cancer) by adopting a tolerance of 5 ppb (currently the lowest enforceable tolerance) as opposed to FDA's proposed tolerance of 15 ppb. This analysis applies to the population at highest risk, namely that of the southeastern United States.

In other areas of the country, where aflatoxin contamination of corn is not a significant problem, the health risks from aflatoxins are due, for the most part, to exposure to contaminated peanuts. The estimated lifetime risk to humans from this source of exposure only, based on the same type of calculations used to derive Table VII, ranges from 0.8 to $2.0/10^5$, if it is assumed that all peanut products contain 1.5 ppb aflatoxins (under the proposed 15 ppb tolerance). This theoretical lifetime risk of cancer would be reduced to $0.5-1.3/10^5$ at a 10 ppb tolerance and $0.3-0.7/10^5$ at a 5 ppb tolerance.

For the convenience of the reader, the lifetime liver cancer incidence rates listed in the foregoing tables are summarized in Table VIII.

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TABLE VIII: Summary of Maximum Expected Lifetime Liver Cancer Incidence Rates Due to Aflatoxin Exposures Under Current FDA Guideline of 20 PPB.

Actual Incidence Rates^{1/}

Total U.S. - 161 per 100,000

Alabama - 100 per 100,000

Georgia - 103 per 100,000

Estimated Incidence Rates Due to Aflatoxins

From Combined Rat Studies^{2/}

Total Consumption: 240 to 1160 per 100,000

Peanut Products Only: 2 to 7 per 100,000

From Combined Animal Studies^{2/}

Total Consumption: 17 to 126 per 100,000

Peanut Products Only: Less than .1 per 100,000

From Epidemiology Studies^{3/}

Total Consumption: 20.2 to 67.0 per 100,000

Peanut Products Only: 1.1 to 2.7 per 100,000

^{1/} See Text, pages 15, 16.

^{2/} See Text, Table V.

^{3/} See Text, Table VII.

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