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April 4, 1978

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To: All Members of:

SPI-VCM/PVC Mailing List (Letter No. 38)
Plastic Bottle Institute
Plastic Beverage Container Group
AN Safety Group
PET Safety Group
Food, Drug and Cosmetic Packaging
Materials Committee
PVC Safety Group

Letter Highlights

(1) FDA has made available an assessment of the risk of liver cancer from aflatoxin contamination of corn and peanut products. Copies are enclosed because of its relevance to estimating the risk associated with other substances such as components of packaging materials.

(2) The risk assessment techniques applied by FDA with regard to aflatoxin are far less conservative than the risk assessments that have been submitted to FDA for food packaging materials.

(3) Data from Professor Maltoni's ingestion studies of acrylonitrile and vinyl chloride have become available and are discussed. Copies of the final acrylonitrile report and excerpts of the vinyl chloride interim report are enclosed.

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(4) "Back-of-the-envelope" type risk calculations indicate that the latest toxicological data will confirm that maximum projected migration of acrylonitrile and vinyl chloride from food packaging materials are well below an "acceptable tolerance level," even if much more stringent criteria than those used in the aflatoxin document are employed. A conservative tolerance level of 16 ppb for products like acrylonitrile copolymer beverage containers and 52-104 ppb for polyvinyl chloride food packaging are estimated.

Ladies and Gentlemen:

As reported in our letter of February 28, 1978, Sherwin Gardner, Deputy Commissioner of Food and Drugs, has informally requested that risk assessments be performed for plastics packaging using the approach being developed by the Food and Drug Administration (FDA) with regard to aflatoxin and lead contamination. Accordingly we are sure you will be interested in reading FDA's newly released "Assessment of Estimated Risk Resulting from Aflatoxins in Consumer Peanut Products and Other Food Commodities," dated January 19, 1978, a copy of which we are enclosing. Notice of the availability of this risk assessment appeared in the Federal Register on March 3, 1978. FDA's risk assessment for lead migration has not been published yet.

We have recently obtained and are enclosing copies of additional information regarding the acrylonitrile and vinyl chloride studies of Professor Maltoni, Director of the Institute of Oncology in Bologna, Italy. These new data are crucial because risk extrapolations can most effectively be performed only when complete data are available.

Aflatoxin Risk Assessment

By comparison to other risk extrapolations that have been submitted to FDA for food packaging materials (PVC and AN copolymers), the FDA assessment of the cancer

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risk posed by aflatoxin could be termed recklessly non-conservative. Indeed, it is hard to compare the FDA assessment of the risk presented by aflatoxin to existing calculations of risk for acrylonitrile or vinyl chloride since FDA's methodology with regard to aflatoxin departs drastically from previously accepted norms with respect to both the mathematical model employed and in the handling of the data.

FDA's risk assessment for aflatoxin concerns itself solely with aflatoxin contamination of corn and peanut products since, according to FDA, these are the only products where such contamination is generally at a detectable level. FDA justifies ignoring the levels of aflatoxin in other food products on the grounds that considering them would not significantly alter the conclusions of the report. We are at a loss to understand why the level of aflatoxin contamination in other foods known to contain aflatoxin is not assumed to be at a level just below the sensitivity of analytical detection methods, an assumption FDA routinely applies to other products.

Another interesting aspect of the risk assessment for aflatoxin is FDA's method of estimating dietary consumption. Although the 90th percentile of consumption is considered, nowhere in the document is there any reference to a gluttonous consumer of peanut or corn products who might make corn or peanuts the major portion or sole constituent of his diet, as was insisted upon by the Government in dealing with carbonated beverages in the hearing on acrylonitrile copolymer beverage containers; nor is any discussion devoted to the risk to a child who eats only peanut butter and jelly sandwiches. From a statistical standpoint, it is, of course, proper to ignore such transient or aberrant dietary practices since they have little significance when assessing the average risk to the entire population over a full life span. It appears that the Commissioner now concurs with this position although he chose to decide otherwise when dealing with beverage containers.

A very significant non-conservatism in FDA's risk assessment concerns the level of confidence associated with its Mantel-Bryan risk extrapolation. In all previous Mantel-Bryan extrapolations on acrylonitrile and vinyl chloride, the toxicological data was conservatively handled (i.e., given a "worst case" interpretation) in a manner that yielded

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a 99% confidence factor for the result. This 99% confidence factor is part of the modified Mantel-Bryan procedure and was adopted by FDA in its Sensitivity of Method Regulation on Carcinogenic Animal Drug Residues. We have not been able to verify independently the confidence limit used in FDA's aflatoxin risk extrapolation, but the discussion on page 11 and the accompanying Table V suggest to us that no such conservative treatment of the toxicological data was applied before performing the Mantel-Bryan extrapolation.

The above comments barely begin to cover the inconsistencies between FDA's risk assessment for aflatoxin and the ultraconservative, by comparison, risk assessments that have been submitted to FDA for residual monomers that unavoidably contaminate plastics packaging materials. Candidly, our general impression is that FDA made unsupported assumptions and distorted the numerical presentations in the aflatoxin document to support the conclusion it wanted to reach.

We considered preparing SPI comments on FDA's aflatoxin risk assessment, but have concluded that such comments would be more appropriate on the risk assessment for lead migration which is being prepared by FDA and should be available shortly. Inasmuch as FDA provided only a brief period for comment with respect to aflatoxin, and suspecting that an equally brief time will be allowed vis-a-vis any lead document, it may not be possible for us to go through normal full-scale clearance procedures with respect to comments on the risk assessment for lead. Nonetheless, we shall proceed on the basis that comments on the lead assessment will be desirable and will endeavor to get draft comments to a cross-section of SPI members for clearance prior to filing.

Risk Assessments for Plastics Monomers

A major criticism of risk extrapolations for both acrylonitrile and vinyl chloride have concerned the fact that they were based on the results of incomplete feeding data in one case and on inhalation data in the other. Professor Maltoni has now completed his ingestion studies of acrylonitrile and vinyl chloride. A final report on the

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acrylonitrile study has been published and we are enclosing a copy for your information. Professor Maltoni concludes that at a level of 5mg/kg administered three times per week, acrylonitrile exhibited a "borderline" oncogenic effect. We are hopeful, but not optimistic, that a final report on vinyl chloride will be forthcoming shortly.

In the meantime, through the very gracious cooperation of one of our members, a monograph presenting (in French) the papers and the ensuing discussions delivered at a Colloquium held in Paris on March 2, 1976, has now become available. Professor Maltoni presented a comprehensive review of his work to that date on vinyl chloride carcinogenicity and a full copy of his paper has been provided to the Food and Drug Administration (FDA). Because of the length of the paper, we cannot distribute it to all of you receiving this letter but we are enclosing copies of pages 25 and 26 of the monograph which report the results of the gavage (stomach tube) feeding experiments to that date.

The conclusions Professor Maltoni drew from the almost completed feeding test (page 26) can be translated roughly as follows:

(1) At 50 and 16.65 mg/kg VCM produces angiosarcomas of the liver and nephroblastomas; these two tumors are the most characteristic produced by the monomer.

(2) At 3.3 mg/kg the two angiosarcomas which have been observed were not located in the liver. (One appeared in the lung, the other near the kidneys.)

(3) There is a clear relationship between dose of monomer and tumor response with a sharp drop-off between 16.65 and 3.33 mg/kg.

Professor Maltoni further stated that in his experiments the 3.33 mg/kg dosage appeared to have a "border line" carcinogenic effect. He then reported that in another experiment in which animals were treated with 1 mg/kg, 0.3 mg/kg and 0.03 mg/kg, no tumors had been observed after 57 weeks into the test.

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In our last letter to the SPI-VCM/PVC Mailing List (Letter No. 37), we discussed the need for completed toxicology studies to provide a sound basis for a risk assessment. Using the FDA risk assessment for aflatoxin as a model, the results of completed long-term feeding studies for acrylonitrile and the most recent vinyl chloride data, we are now in a better position to calculate the risk associated with residual monomers that contaminate food packaging on a basis comparable to that used by FDA. As crude examples (the following should be considered to be merely illustrative and not definitive since it is based on the still incomplete Maltoni data for vinyl chloride and rule-of-thumb calculations) of how a Mantel-Bryan risk evaluation might work, Dr. Dixler has estimated the dietary concentrations for vinyl chloride and acrylonitrile that assure a risk to humans of no more than one in one hundred million (10^{-8}). You may recall that FDA used a risk level of 10^{-6} in its Regulation on Carcinogenic Animal Drug Residues. Because of conservatism in the procedure, however, FDA has stated that the risk presented by its sensitivity of method approach is no more than 10^{-8} .

Vinyl Chloride

Assume that the final Maltoni data for vinyl chloride indeed demonstrates that 3.33 mg/kg administered between four and five days a week is a "no effect" level. Since the vinyl chloride was administered only four to five days a week, we shall assume that the daily dose was 4.5/7ths of 3.33 mg/kg or 2.14 mg/kg. Applying the usual Mantel-Bryan "worst case" assumptions, it can be roughly estimated that, at a 99% confidence level, 2.14 mg/kg would "produce" 4.5 cancers in 100 (4.5%). The Mantel-Bryan "safe" dose at a risk of one in one hundred million is approximately 1/8300 of the dose that causes a 4.5% incidence of cancer. Therefore, a dietary intake of 2.14 divided by 8300 or 0.00026 mg/kg could be deemed "safe" as a total dietary exposure.

Depending upon the assumptions used to convert mg/kg of body weight in the rat to parts per million (ppm) in the total diet in man, 0.00026 mg/kg is equivalent

to 5.2-10.4 parts per billion (ppb) as the safe total dietary exposure for man. Since one can very conservatively assume that PVC could not package more than 10% of the diet, an actual migration level of ten times the safe exposure level could be set as a "tolerance." This tolerance (not more than 52-104 ppb migrating to food) assures that the risk of cancer could not exceed one in one hundred million. In this light, it would certainly seem reasonable to us that a finding of "non-detectable" with an analytical method sensitive to 2 ppb should be deemed to assure virtually absolute safety.

Acrylonitrile

A similar exercise for acrylonitrile, assuming that 5 mg/kg administered thrice weekly is a "no effect" level, also gives an approximate safe total dietary exposure for rats of 0.00026 mg/kg. For a 60 kg (132 lb) person, this is equivalent to a daily intake of 0.0156 mg, as posing a risk no higher than one in one hundred million. Based on the 90th percentile for carbonated beverage consumption (1 liter/day) and assuming all such consumption were from acrylonitrile copolymer packaging, the acceptable migration tolerance would be 16 ppb. If we make the more reasonable assumption that no more than 50% of the carbonated beverage consumption were packaged in AN copolymer containers, a tolerance of 31 ppb would assure virtually absolute safety. Here again, the present analytical sensitivity of 10 ppb is sufficient to reduce any risk from AN to below any meaningful level.

We are sure you will recognize that the foregoing exercises in arithmetic are provided merely to show how important completed toxicology studies are in order to provide a firm basis for risk assessments. In addition to animal studies, FDA would also consider such epidemiological data as can be presented, as well as other methods than the Mantel-Bryan procedure for extrapolating from observed risks at high exposure levels to estimated risks at infinitesimal exposure levels, as was done for aflatoxin.

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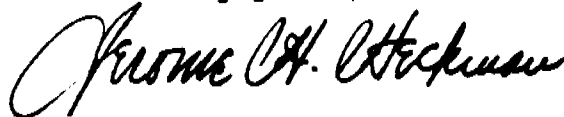
The risk that society might accept for a food packaging material may well be less than the risk considered acceptable for aflatoxin in food. Be that as it may, justice would seem to require that the relevant risk assessments be carried out in a consistent fashion or one is left trying to compare apples to oranges. Even with the biased comparison, the conservative risk assessments that have been done for acrylonitrile and vinyl chloride predict a risk orders of magnitude lower than that accepted by FDA for aflatoxin. It appears that if the acrylonitrile and vinyl chloride data were treated in a manner consistent with the FDA risk assessment for aflatoxin, the estimated risk associated with such food packaging would have to be deemed unworthy of any concern.

There must be a finite level of risk that can be accepted for food packaging since it clearly has social utility. Even such staunch defenders of the public health as Senator Edward Kennedy (D.-Mass.), have now publicly recognized that absolute safety is unattainable. A copy of a speech given by Senator Kennedy at an FDA/EPA Symposium on risk-benefit which appeared in the Congressional Record is enclosed.

It appears, therefore, that recent data concerning the toxicology of acrylonitrile and migration potential (or lack thereof) for vinyl chloride, as well as public and legislative opinion are beginning to realign in a way that may yet make it possible for FDA to acknowledge the existence of a slight risk with respect to packaging materials in general, and that the risk from assumed acrylonitrile or vinyl chloride (and ultimately for any other residual monomer that becomes a concern) migration is trivial and not worthy of regulatory attention.

We shall, as usual, keep you up-to-date regarding the various regulatory activities relating to vinyl chloride polyvinyl chloride and acrylonitrile. In the meantime, those of you who require a complete copy of Professor Maltoni's paper are requested to contact us so we can make special arrangements with you to make it available.

Cordially yours,



Enclosures

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

BUREAU OF FOODS
FOOD AND DRUG ADMINISTRATION
January 19, 1978

ASI-PR 0002633

SUMMARY

Although direct proof that aflatoxins (B_1 , B_2 , G_1 , G_2) 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.

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

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,

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.

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

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

this assessment, the most relevant toxicity data would be those relating 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.

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.

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 ($B_1 + B_2 + G_1 + G_2$)

<u>Food Class</u>	<u>Estimated Average Level</u> (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

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.

DAILY AFLATOXIN INTAKE

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.

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.

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

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.

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	43.0
Swaziland - Lowveld	9.7	43.1
Mozambique - Inhambane	13.0	222.4

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 ^{1/}

PEANUTS ^{2/}			CORN ^{3/}			TOTAL	
Aflatoxin Level	Risks Resulting From Daily Intake ^{4/}		Aflatoxin Level	Risks Resulting From Daily Intake ^{4/}		Risks Resulting From Daily Intake ^{4/}	
(ppb)	Average	Maximum	(ppb)	Average	Maximum	Average	Maximum
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.

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 1.3 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.

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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Estratto da « *La Medicina del Lavoro* »

Vol. 68 - N. 6 - 1977

TIPOLITO MATTIOLI - FIDENZA

ASI-PR 0002661

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1) INTRODUCTION

Acrylonitrile (AN), or Vinyl Cyanide, $C_3H_3.5N$, has the following physical and chemical properties.

Physical state: clear, colorless, volatile, liquid.

Molecular weight: 53.06,

Specific gravity: 0.8004 (25/4° C.),

Freezing point: -83° C.,

Boiling point: 77.3° C.,

Refractive index: 1.3885 (25° C.),

Vapor density: 1.9 (air = 1),

Vapor pressure: 110-115 mm. Hg (25° C.),

Per cent in "saturated air": 14.5 (25° C.),

Density of "saturated air": 1.13 (25° C.) (air = 1).

Solubility: mixible with most common organic solvents, including acetone, benzene, carbon tetrachloride, ether, ethyl acetate, ethylene cyanohydrin, methanol, petroleum ether, toluene, xylene and some kerosenes.

AN is a very versatile and industrially important chemical intermediate. Its reactions may involve the cyano (CN) group alone, the activated double bond ($C=C$), or both groups.

The most important reaction, commercially is its polymerization: in fact it is used mainly (95% of the total use) as a monomer or a comonomer (with styrene and butadiene) for the production of synthetic textile fibers, plastics and rubber elastomers. AN gives important properties to polymeric materials:

ability to form oriented fibers; and impact, thermal, chemical, solvent and weather resistance.

It also undergoes many reactions to form compounds used as solvents, plasticizers, and dyes, pharmaceutical and insecticide intermediates. AN has, moreover, other different uses. For example, cyanoethylated natural fibers (cotton) could develop into products of major importance.

AN is produced in various countries of Europe, Americas, Asia, and Africa. The major producers are Western Europe, U.S.A. and Japan. The whole present production is estimated to be 2,8 million tons per year.

The monomer may easily be absorbed by inhalation, ingestion and through intact skin. It has long been known to possess a high degree of toxicity, which has many of the characteristics of poisoning by cyanide ion. Several studies on the toxic effects in a variety of species of experimental animals have been performed.

Some value of the toxic effects produced when given by inhalation are listed in table 1.

TABLE 1 - Toxic effects produced by AN given by inhalation, on different animal species (from PART, 1965).

Animal	Concentration (ppm)	Response
Rat	636	Fatal after 4 hrs. exposure
Rat	129	Slight transitory effects
Rat	97	Slight transitory effects
Rabbit	258	Fatal during or after exposure
Rabbit	133	Marked transitory effects
Rabbit	97	Slight transitory effects
Cat	276	Markedly toxic
Cat	152	Markedly toxic, sometimes fatal
Guinea pig	576	Fatal during or after exposure
Guinea pig	267	Slight transitory effects
Dog	110	Fatal to three fourths of the dogs
Dog	98	Convulsions and coma; no death
Dog	55	Transitory paralysis; 1 dog died
Dog	29	Very slight effects

Orally, the LD_{50} in the mouse is of the order of 35 mg/Kg; in the rat, about 78 mg/Kg; and in the guinea pig, about 90 mg/Kg. Rats ingesting 0.1 per cent in water for a period of 13 weeks showed retarded growth and emaciation; some effects were also noted with as low as 0.05 per cent in water in 2-year feeding studies.

There is considerable variation in resistance to acrylonitrile exposure in different species. Guinea pigs seem to be the most resistant to the toxic effects of acrylonitrile, while dogs are the least resistant. Toxic effects of acrylonitrile which have been noted in animals include damage to the central nervous system, lung, liver and kidneys. When administered to pregnant mice, acrylonitrile has been found to be embryotoxic (SHEUFLER, 1976).

In man, AN is toxic by inhalation, oral ingestion and skin penetration. It causes a sequence of symptoms whose gravity parallels the degree of exposure: weakness, headache, sneezing, nausea, abdominal pain, vomiting, loss of consciousness and asphyxia. It may also cause skin irritation, particularly when the skin is exposed to clothing or shoes wet with the chemical. AN, in contact with the surface of the eye, produces severe irritation or mild burns.

The following population groups may be potentially exposed to AN:

- 1) workers engaged in the production of AN monomer;
- 2) workers manufacturing and processing AN products on an industrial scale;
- 3) residents around factories producing AN and AN products; and
- 4) to a much lesser extent, people undergoing contact with AN products and materials containing these products, and finally;
- 5) consumers of food stocked in material made with AN plastics.

Until 1974 there were no available studies on the carcinogenicity of AN. At that time a project of long-term carcinogenicity bioassays on rats was planned. The project was supported by a group of European Producers of AN (European Study Group for AN toxicity)*.

The research was started at the end of 1974.

2) PLANNING, MATERIAL AND METHODS

Our project includes experiments designed to study the long-term effects of AN, administered by different routes (inhalation and ingestion), at different concentrations (when given by inhalation), on rats.

The chambers for inhalation exposure are basically built of stainless steel and glass. The control of AN concentrations is carried out by gas chromatography.

For the ingestion experiments AN was administered in olive oil by gavage with a stainless steel stomach tube.

* Rhône-Poulenc, Ugine Kuhlman (France); BASF, Bayer, Hoechst (Germany); DSM (Holland); Montedison, ANIC, SIR-Rumianca (Italy); BP (U.K.).

AN was supplied and analyzed by the Central Laboratory of Montedison (Italy). The impurities and their levels in the AN employed were as follows:

Acrylonitrile	: > 999%
Acetonitrile	: Traces
Acrolein	: Traces
Hydroquinone monomethyl ether:	100 ppm.

The experiments utilized Sprague-Dawley rats. The animals have been bred in our Institute for years, and whatever their use, are all examined at death by complete autopsy, giving us extensive information concerning their current pathology.

The animals were weaned and classified by sex when 4-5 weeks old, at which time they were numbered by ear punch and divided into group by litter distribution. After weaning, the animals were fed, ad libitum, with an adequate commercial diet. The animals were kept in groups of five, in macrolon* cages, with tops made of stainless steel wire, but, during the period of inhalatory treatment, they were housed in groups of ten in stainless steel wire cages with a solid bottom of the same metal. A shallow layer of white wood shavings served as bedding. The animals were kept in a temperature-controlled laboratory at 19-20° C.

Two experiments were started around the same period. The plan of the experiments is given in tables 2, 3.

Experiment 1 (BT201): studies the effects on rats of inhalation exposure to 40, 20, 10 and 5 ppm of AN, 4 hours daily, 5 days weekly, for 12 months.

One group of untreated animals served as control.

Experiment 2 (BT203): was designed to evaluate the effects on rats of AN, administered by stomach tube, in olive oil, at a single daily dose of 5 mg/Kg body weight, 3 times weekly, for 52 weeks. One group of animals, receiving olive oil alone by the same route, and in the same quantity, served as control.

The animals were controlled weekly, and weighed every 2 weeks during the period of treatment and monthly after the treatment was over. All the detectable gross pathological changes were recorded during the control. All the animals were kept under observation until spontaneous death. The animals, when moribund, were isolated, in order to avoid cannibalism.

A complete autopsy was carried out on each animal. Histological examinations were performed in the Zymbal glands, interscapular brown fat, salivary glands, tongue, lungs, liver, kidneys, spleen, stomach, different segments of the intestine, bladder, brain, and any other organs with pathological lesions.

3) RESULTS AND COMMENTS

Both experiments have now ended and complete examination of biological data and of the histopathologic material has been performed.

* polycarbonate.

TABLE 2 - Experiment BT201: Exposure by inhalation to Acrylonitrile (AN) in air at 40, 20, 10, 5 ppm, 4 hours daily, 5 days weekly, for 52 weeks. Results after 136 weeks (end of the experiment).

(first part)

GROUP NO.	TREATMENT		ANIMALS (Sprague-Dawley 90% 12 weeks old at start)		Corrected number (n)	ANIMALS WITH TUMORS															Cystic gland carcinoma		
						Mammary tumours																	
						Histological types																	
						No.	% (a)	Average latency time (weeks) (c)	Average latency time (weeks) (c)	Latency time (weeks) (c)	No.	% (a)	Average latency time (weeks) (c)	Average latency time (weeks) (c)	Latency time (weeks) (c)	No.	% (a)	Average latency time (weeks) (c)					
I	40 ppm	52	Q	20	20	7	35.0	11.5	1.4	5	10.0	10.0	1.4	7	6.6	77.0	10.0	-	-	-			
			Q	20	20	4	20.0	11.5	1.0	1	10.0	10.0	1.0	1	3.3	58.0	10.0	-	-	-			
			Q and Q	40	40	11	27.5	11.5	1.1	6	15.0	10.0	1.2	1	5.0	60.7	10.0	-	-	-			
II	20 ppm	52	Q	30	30	10	33.3	10.5	1.0	5	10.0	10.0	1.0	1	3.3	75.0	10.0	1	3.3	71			
			Q	30	30	4	13.3	11.5	1.0	2	6.6	10.0	1.0	2	6.6	15.0	10.0	-	-	-			
			Q and Q	60	60	14	23.3	10.5	1.0	11	18.3	10.0	1.0	3	5.0	49.3	10.0	1	1.6	71			
III	10 ppm	52	Q	30	30	7	23.3	10.5	1.4	3	10.0	10.0	1.4	-	-	-	-	1	3.3	101.0			
			Q	30	30	-	-	-	-	1	3.3	10.0	1.0	-	-	-	-	1	3.3	104.0			
			Q and Q	60	60	7	11.7	10.5	1.4	4	11.1	10.0	1.4	-	-	-	-	2	3.3	102.5			
IV	5 ppm	52	Q	30	30	10	33.3	9.2	1.2	6	20.0	9.0	1.1	4	13.3	51.0	10.0	-	-	-			
			Q	30	30	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
			Q and Q	60	60	1	16.6	9.2	1.2	6	10.0	9.0	1.1	4	6.6	51.0	10.0	-	-	-			
V	None (Control)	52	Q	30	30	5	16.6	94.0	1.0	4	13.3	93.0	1.0	1	3.3	95.0	10.0	-	-	-			
			Q	30	30	1	3.3	115.0	1.0	-	-	-	-	1	3.3	115.0	10.0	-	-	-			
			Q and Q	60	60	6	10.0	100.5	1.0	4	6.6	93.0	1.0	2	3.3	116.5	10.0	-	-	-			
Total				100	100																		

(a) Alive animals after 2 weeks, when the first tumour (a mammary carcinoma) was observed.

(b) The percentages are referred to the corrected number.

(c) The latency time of mammary tumours is given as age; the latency time of the other tumours is given as period from the start of the experiment.

TABLE 2 - Experiment BT201: Exposure by inhalation to Acrylonitrile (AN) in air at 40, 20, 10, 5 ppm, 4 hours daily, 5 days weekly, for 52 weeks.
Results after 136 weeks (end of the experiments).

(second part)

GROUP		ANIMALS WITH TUMORS																									TOTAL (n)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
		Forelimb pad pilonary and adenoma			Incapsule tumours												Skin carcinomas			Uterine carcinomas			Others																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																			
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					No.	% (b)	Average latency time (weeks) (c)	No.	% (b)	Average latency time (weeks) (c)	No.	% (b)	Average latency time (weeks) (c)	No.	% (b)	Average latency time (weeks) (c)										No.		% (b)	Average latency time (weeks) (c)	No.	% (b)	Average latency time (weeks) (c)	No.	% (b)	Average latency time (weeks) (c)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																							
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(d) 1 inguinal.

(e) 1 of the face.

(f) 1 maxillary.

(g) 1 maxillary.

(h) 1 paracard; 1 inguinal; 2 near the anus.

(i) 1 fibroma of skin; 1 subcutaneous fibrosarcoma; 1 adrenal adenocarcinoma; 1 squamous cell carcinoma of bladder; 1 leukæmia.

(j) 1 subcutaneous lipoma; 1 adenoma of hypophysis; 1 adenocarcinoma of ovary; 1 leukæmia.

(k) 1 Zymbal gland adenoma; 1 fibroma of skin; 1 fibrosarcoma of skin; 1 subcutaneous fibrosarcoma; 1 lipoma near the caecum; 2 leukæmias.

(l) 1 Zymbal gland adenoma; 1 squamous cell carcinoma of stomach; 1 adenocarcinoma of pancreas; 1 adrenal adenoma; 1 theca cell tumor of ovary; 1 fibrosarcoma of uterus; 1 fibromyoma of uterus.

(m) 1 subcutaneous fibrosarcoma; 1 neoplasm of skin; 1 adrenal carcinoma; 2 adrenal adenomas; 2 leukæmias.

(n) 2 adenomas of hypophysis; 1 adrenal adenoma.

(o) 1 subcutaneous angioma; 1 subcutaneous fibrosarcoma; 2 adrenal adenocarcinomas.

(p) 1 fibroma of skin; 1 subcutaneous fibrosarcoma; 2 adrenal adenomas.

(q) Several animals with 2 or more tumors.

TABLE 3 - Experiment BI203: Exposure by ingestion (stomach tube) to Acrylonitrile (AN) in olive oil at 5 mg/Kg body weight, 3 times weekly, for 52 weeks. Results after 131 weeks (end of the experiment). (first part)

GROUP NO.	TREATMENT	Length (weeks)	ADULTS (Sprague-Dawley strain, 12 weeks old at start)		Corrected number (a)	ANIMALS WITH TUMOURS																	
			Sex	No. at start		No.	♂ (b)	Average latency time (weeks) (c)	No. of tumours/animal	Histotypes													
										Fibrosarcomas and fibromas				Carcinomas					Fibrosarcomas and carcinomas				
										No.	♂ (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	♂ (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	♂ (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal		
I	5 mg/Kg	52	Q	40	40	21	52.5	61.5	1.4	18	45.0	82.5	1.4	2	5.0	61.0	1.0	1	2.5	108.0	0.5		
			O	40	40	2	5.0	81.0	1.0	-	-	-	-	-	-	-	-	-	-	-			
			Q and O	80	80	23	28.7	60.2	1.3	20	25.0	82.5	1.3	2	2.5	61.0	1.0	1	1.2	108.0	0.5		
II	None (Controls)		Q	82	75	33	44.0	62.0	1.4	26	34.5	85.2	1.5	4	5.3	77.5	1.0	3	4.0	68.6	1.7		
			O	77	74	2	2.7	77.0	1.0	-	-	-	-	-	-	-	-	-	-	-			
			Q and O	159	149	35	21.2	62.4	1.4	26	17.5	84.6	1.4	4	2.7	77.5	1.0	3	2.0	68.6	1.7		
Total				239	229																		

(a) Alive animals after 28 weeks, when the first tumour (a mammary carcinoma) was observed.

(b) The percentages are referred to the corrected number.

(c) The latency time of mammary tumours is given as age; the latency time of the other tumours is given as period from the start of the experiment.

TABLE 3 - Experiment BT203: Exposure by ingestion (stomach tube) to Acrylonitrile (AN) in olive oil at 5 mg/Kg body weight, 3 times weekly, for 52 weeks.
Results after 131 weeks (end of the experiment).

(first part)

GROUP	TREATMENT		ANIMALS (Sprague-Dawley rats, 12 weeks old at start)		Corrected number	ANIMALS WITH TUMOURS													
						Mammary tumours								Histotypes					
						Fibroadenomas and fibromas				Carcinomas				Fibroadenoma and carcinoma					
						No.	% (a)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)	Average latency time (weeks) (c)	Mean No. of tumours/animal	No.	% (b)
I	5 mg/Kg	52	♀	40	40	21	52.5	61.1	1.4	18	45.0	82.3	1.4	2	5.0	61.0	1.0	1	2.5
			♂	40	40	2	5.0	61.0	1.0	2	5.0	81.0	1.0	-	-	-	-	-	-
			♀ and ♂	80	80	23	28.7	60.2	1.3	20	25.0	82.6	1.3	2	2.5	61.0	1.0	1	1.2
II	None (Controls)		♀	82	75	33	44.0	62.6	1.4	26	34.7	85.2	1.5	4	5.3	77.5	1.0	3	4.0
			♂	77	74	2	2.7	77.3	1.0	2	2.7	77.3	1.0	-	-	-	-	-	-
			♀ and ♂	159	149	35	23.2	65.4	1.4	28	18.8	84.6	1.4	4	2.7	77.5	1.0	3	2.0
Total				239	229														

- (a) Alive animals after 28 weeks, when the first tumour (a mammary carcinoma) was observed.
 (b) The percentages are referred to the corrected number.
 (c) The latency time of mammary tumours is given as age, the latency time of the other tumours is given as period from the start of the experiment.

Under our experimental conditions AN, administered both by inhalation and ingestion, had shown no effects on the survival and body weight of the animals. No regressive histological changes had taken place in liver, kidneys and lung.

As far as neoplasias are concerned, their incidence in treated and controls groups of inhalation and ingestion experiments is given in tables 2 and 3. Several types of tumours have been observed.

Among the most frequent there are mammary tumours, Zymbal gland carcinomas, forestomach papillomas and acanthomas, encephalic tumours, skin carcinomas and uterin carcinomas.

Mammary tumours. A moderate increase of mammary tumours has been observed in both experiments, in the treated groups, however without a clear-cut dose-response relationship and significant shortening of the average latency time.

Zymbal gland carcinomas. Only a few of these neoplasias have been observed. On the whole, the distribution in the treated and control groups is not significant.

Forestomach papillomas and acanthomas. A moderate increase of these tumours has been found in the treated groups of both experiments.

Encephalic tumours. As far as these tumours are concerned, a systematic histological investigation on serial sections has been performed on animals in the treated groups as well as in the control groups. Systematic histology was made necessary since these tumours are not grossly detectable. These tumours have been found in AN treated (BT201, BT203) as well as in control animals, treated with olive oil alone (BT203).

All the 4 tumours observed in the treated animals and 3/5 of the ones in the controls were gliomas (Fig. 1 and 2).

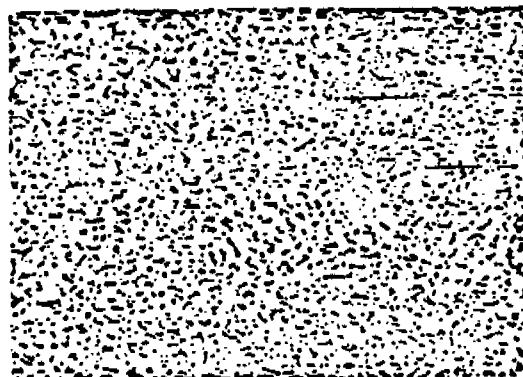


Fig. 1 - Encephalic glioma in a rat exposed by inhalation to 40 ppm of AN. H.E., $\times 125$.



Fig. 2 - Encephalic glioma (peripheral area) in a rat exposed by inhalation to 40 ppm of AN. H.E., $\times 125$.

Two data have to be underlined.

1) The tumours observed in the animals treated with AN by inhalation have been found in the animals treated at the highest doses (40 and 20 ppm);

2) The incidence of tumours in control animals (experiment BT203) has been surprisingly high.

To our knowledge, there is no adequate systematic research on the spontaneous incidence of tumours of the central nervous system in experimental rodents.

Therefore, histologic research has been extended to comparable control rats of uncorrelated experiments, not treated at all. Over 403 examined rats 13 tumours have been observed: 4 gliomas, 2 ependymomas and 7 meningiomas.

Skin carcinomas. The onset of a few skin carcinomas has been found among the animals treated by AN, administered by inhalation.

Uterine carcinomas. On the whole there are no significant difference among treated animals and control groups.

4) CONCLUSIONS

On the basis of the presented results it may be stated that under our experimental conditions, AN has shown a border-line oncogenic effect.

At present our data do not make definitive evaluations possible. On the other hand, they point to the need of further investigations on the long-term effects of AN.

In particular the following investigations are foreseen:

- 1) the study of the effect of AN, given by inhalation and ingestion at a single dose level chosen on the basis of our present knowledge, on large groups of rats, with adequate controls;
- 2) the study of the effect of AN, administered at least by one route (possibly inhalation), on animals of another species (mouse);
- 3) a histologic research on a large number of untreated rats of our breed to better assess the spontaneous background incidence of encephalic tumours. On a wider scale, this type of study should be extended to other rodents commonly used in experimental bioassays, since our knowledge in this field is rather limited.

SUMMARY

The present report deals with the results of long-term carcinogenicity bioassays of Acrylonitrile (AN), which lasted more than 130 weeks.

The monomer has been tested on rats by inhalation (40, 20, 10, 5 ppm, 4 hrs daily, 5 times weekly, for 52 weeks), and by ingestion (5 mg/Kg body weight, in olive oil, by stomach tube, once daily, 3 times weekly, for 52 weeks).

A slight enhancement of the incidence of some tumours has been reported and commented. At present no sound conclusions can be drawn, on the basis of the present data.

The need of further research is stressed.

RIASSUNTO

MALTONI C., CILIBERTI A., DE MAIO V. — *Saggi sperimentali di cancerogenicità dell'Acronitrile, somministrato per inalazione e per ingestione, sul ratto.*

Vengono riferiti i risultati dei saggi di cancerogenicità a lungo termine dell'Acronitrile (AN), durati più di 130 settimane. Il monomero è stato saggiato su ratti per inalazione (40, 20, 10, 5 ppm, 4 ore al giorno, 5 volte alla settimana, per 52 settimane), o per ingestione (5 mg/Kg peso corporeo, in olio di oliva, mediante sonda gastrica, 1 volta al giorno, 5 volte alla settimana, per 52 settimane). È stata osservata e valutata una modica incidenza di alcuni tumori. Al momento presente, sulla base delle risultanze presentate, non possono essere tratte conclusioni definitive. Viene sottolineata la necessità di un piano di ulteriori ricerche.

REFERENCES

SCHNEUFELER H. (1976) - *Biol. Rundsch.*, 14, 227-229.

du moins en ce qui concerne les angiosarcomes et les néphroblastomes, est affectée par la longueur de l'exposition au CVM.

La comparaison des résultats obtenus chez le rat de deux différentes lignées (Sprague Dawley BT1 et Wistar BT7) suggère actuellement que le facteur souche affecte de la même façon la réponse néoplasique.

La survenue de 4 angiosarcomes extra hépatiques, d'un néphroblastome et de 4 cancers de la glande de Zymbal dans les portées de femelles exposées au cours de la gestation pendant 7 jours, semble montrer un effet transplacentaire du CVM.

L'observation de quelques cas d'angiosarcomes osseux suggère une nouvelle orientation dans l'interprétation pathogénique de l'acrostéolyse des os chez les animaux exposés au CVM.

Pr LATAJET - Les tumeurs mammaires ont-elles été observées chez les femelles seulement ?

Pr MALTONI - Oui.

Dr ZAJDELA - Dans quelle lignée de souris ?

Dr MALTONI - Souris Suisse.

Dr ZAJDELA - C'est une lignée que vous élevez chez vous ?

Pr MALTONI - Oui, depuis 1963.

Dans nos conditions d'expérience, le chlorure de vinyle, lorsqu'il est administré par ingestion (gavage) (tableau 19), produit chez le rat des angiosarcomes du foie et d'autres localisations, des néphroblastomes et des cancers de la glande de Zymbal. On soulignera cependant que les doses produisant des tumeurs sont très élevées, lorsqu'on les compare à l'exposition possible chez l'homme.

TABLEAU 19

Expérimentation BT11 : Exposition par ingestion (gavage) au CVM en huile d'olive, à 50, 16,65, 3,33 mg/kg poids corporel, une fois par jour, 4-5 j./semaine, 52 semaines. Résultats après 104 semaines.

GROUPES ET TRAITEMENT	ANIMAUX (RATS SPRAGUE- DAWLEY)		ANIMAUX AVEC TUMEURS						
			Carcinomes de la glande de Zymbal	Néphro- blastomes	Angiosarcomes		Carci- nômes mammaires	Autres types et/ou localisations (c)	Total
					Foie	Autres locali- sations			
	Total	Survivants	N.	N.	N.	N.	N.	N.	N.
I CVM 50,00 mg/kg	80	6	1	1	13	1 (a)	3	4 (d)	22 (g)
II CVM 16,65 mg/kg	80	10	1	3	6	-	5	1 (e)	15 (g)
III CVM 3,33 mg/kg	80	20	-	-	-	1 (b)	2	2 (f)	5
IV Contrôle: huile d'olive	80	13	-	-	-	-	2	-	2
Total	320	49	2	4	19	2	12	7	44

a) 1 angiosarcome du thymus.

b) 1 angiosarcome intra-abdominal (près du rein).

c) Des cas de fibroadénomes mammaires et de tumeurs surrénales et pituitaires (généralement adénomes) n'ont pas été pris en considération; leur distribution dans les différents groupes n'étant pas significative.

d) 1 carcinome cutané sébacé; 2 papillomes du pré-estomac; 1 adénocarcinome intestinal.

e) 1 lymphome.

f) 1 sarcome sous-cutané avec composante angiomateuse; 1 sarcome intra-abdominal ossifiant avec composante angiomateuse.

g) 1 animal avec 2 tumeurs.

Au moment de mettre sous presse ce compte rendu début Juillet, on pouvait disposer de données de l'expérimentation BT 11, à la date du 21 Juin, c'est-à-dire 120 semaines après son début, alors que l'expérimentation en était presque à la fin (seulement 12 animaux survivants).

Compte tenu du grand intérêt de ces résultats on a jugé important de rapporter ces derniers résultats (tableau 20).

TABLEAU 20

Expérimentation BT11 : Exposition par ingestion (gavage) au CVM en huile d'olive, à 50, 16.65, 3.33 mg/kg poids corporel, une fois par jour, 4-5 j./semaine, 52 semaines. Résultats après 120 semaines.

GROUPES ET TRAITEMENT	ANIMAUX (RATS SPRAGUE- DAWLEY)		ANIMAUX AVEC TUMEURS						
			Carcinomes de la glande de Zymbal	Néphro- blastomes	Angiosarcomes		Carci- noms mammaires	Autres types et/ou localisations	Total (g)
	Total	Survivants			Foie	Autres locali- sations			
			N.	N.	N.	N.	N.	N.	N.
I CVM 50.00 mg/kg	80	2	1	2	16	2 (a)	5	7 (c)	29
II CVM 16.65 mg/kg	80	2	2	3	9	-	6	3 (d)	21
III CVM 3.33 mg/kg	80	4	-	-	-	2 (b)	4	3 (e)	9
IV Contrôle : huile d'olive	80	4	1	-	-	-	4	5 (f)	9
Total	320	12	4	5	25	4	19	18	68

a) 1 angiosarcome du thymus ; 1 angiosarcome intra-abdominal (près de la rate).

b) 1 angiosarcome du poumon ; 1 angiosarcome intra-abdominal (près du rein).

c) 1 carcinome cutané sébacé, 1 hépatome ; 1 angiome du foie ; 2 papillomes du pré-estomac, 1 adénocarcinome intestinal ; 1 lymphome.

d) 1 angiome du foie, 1 carcinome surrénal ; 1 lymphome.

e) 1 sarcome sous-cutané avec composante angioblastique ; 1 sarcome intra-abdominal ossifiant avec composante angioblastique, 1 papillome de la vessie.

f) 1 carcinome cutané ; 1 papillome du canal auditif ; 1 carcinome de la vessie ; 1 carcinome surrénal ; 1 sarcome réticulaire.

g) Plusieurs animaux avec 2 tumeurs.

De leur analyse on peut tirer actuellement quelques conclusions :

- 1) A 50 et 16.65 mg./kg., le CVM produit des angiosarcomes du foie et des néphroblastomes, qui sont les deux tumeurs les plus typiques produites par le monomère.
- 2) A 3.33 mg./kg., les 2 angiosarcomes observés avaient une localisation extra-hépatique.
- 3) Il existe une relation très nette entre dose de monomère et la réponse tumorale, avec une chute entre 16.65 et 3.33 mg./kg.

En comparant les résultats obtenus dans les groupes traités avec 50 et 16.65 mg./kg., dans les

groupes traités avec 3.33 mg./kg., et dans les témoins, la dose de 3.33 mg./kg. dans nos conditions expérimentales, semble avoir un effet carcinogénique « border-line »

Aucune tumeur n'a été observée jusqu'à présent, c'est-à-dire à 57 semaines du début de l'expérimentation, dans les animaux traités avec 1mg/kg, 0.3mg/kg. et 0.03mg/kg. (expérimentation BT27).

Cette dernière expérimentation fut commencée au moment où l'on observait les deux premiers angiosarcomes dans les animaux de l'expérimentation BT11, traités avec 50 et 16.65 mg./kg.

Soviet Jews and to allow all Soviet Jews to exercise their right to emigrate.

Section 2. That this Board urges the appropriate officials of the Soviet Union to grant to Anatoly Shcharansky and his wife the right to emigrate and be reunited with his wife to Anatoly Shcharansky as guaranteed by the Helsinki Accord, 1975; and that if the Soviet authorities bring Anatoly Shcharansky to trial, that he be given an open and public trial, and that prominent representatives of major Bar associations and of the Criminal Bar of the United States be permitted to be present throughout the trial of Anatoly Shcharansky. ©

TURKISH VIOLATIONS OF HUMAN RIGHTS

HON. NEWTON I. STEERS, JR.

OF MARYLAND

IN THE HOUSE OF REPRESENTATIVES

Wednesday, March 15, 1978

Mr. STEERS. Mr. Speaker, this year, the House will be considering the question of foreign assistance to Turkey. At the base of this debate is the question of whether or not the human rights record of Turkey has improved.

A constituent of mine, Mr. George Spring, has sent me an interesting article on this very subject that I would like to insert into the CONGRESSIONAL RECORD for the benefit of my colleagues.

A "DELIBERATE WHITEWASH" ON HUMAN RIGHTS IN TURKEY (By Jack Anderson)

The Carter administration is so worried about declining Turkish military power that it has falsified its report on human rights practices in Turkey and has portrayed the country as a virtual human rights paradise.

The false account, part of the State Department's "Country Reports on Human Rights Practices," was delivered to Congress several weeks ago. The department claimed it had little "conclusive proof" or "significant evidence" to support allegations of human rights abuses in Turkey.

A more enigmatic statement, worthy of master diplomat Henry Kissinger, was issued on Turkish-controlled northern Cyprus. Human rights questions in Cyprus, stated the report, "cannot be treated in isolation from political considerations."

These conclusions are disputed by the State Department's own files, which contain abundant evidence of the harsh treatment of minority groups and political prisoners. Indeed, the Turks have a reputation for brutality, which makes them fierce fighters and cruel jailers.

American citizens, who have had the misfortune of landing in a Turkish lockup, have told of vicious beatings. A favorite Turkish torture is to batter the soles of a prisoner's feet with truncheons, which causes excruciating pain and leaves him unable to walk.

The Greek government, taking exception to the State Department's fairy tale, lodged formal protests both in Athens and Washington. And Cypriot Ambassador Nicos Dimitriou marched into the State Department and indignantly delivered an official letter of protest.

The official view of human rights in Turkey, insiders suspect, is a deliberate whitewash intended to tip-toe around Turkish sensitivities. The Turks are still smarting from an arms embargo imposed by Congress after Turkish troops invaded Cyprus with U.S. weapons.

The Turks retaliated by closing U.S. intelligence installations in their country. These electronic listening posts monitored Soviet missile tests and military maneuvers. At Sinop on the Black Sea, for example, sophisticated radar devices could zoom directly on Soviet missile launch sites.

At the time the bases were closed, intelligence sources claimed they were responsible for about a fourth of the clandestine information gathered about Soviet military activities. American technology and ingenuity, however, have produced substitutes for most of the Turkish installations.

Far more important, in the Pentagon's view, is Turkey's role as the Mediterranean anchor of the NATO alliance. One worried general told us: "The big question is whether they can perform their NATO responsibilities without military aid. We get a real buy with the Turks. Give them a few weapons, and you buy a bunch of divisions. They've got the manpower, and they proved they could use it in the Korean War."

Our sources say that President Carter has adopted the military view. He has been strongly influenced by the joint chiefs, who meet with him frequently. In fact, the president recently boasted to his Cabinet behind closed doors that he "has generated a compatibility among the strategic planners of our government unknown in former administrations."

He reportedly is preparing, therefore, to ask Congress to approve the \$1-billion defense agreement that was signed in 1976 between Turkey and the United States. The State Department soft-pedaled Turkish human rights abuses, our sources say, to avoid irritating a Congress that is already sympathetic to the Greek and Cypriot causes.

In any event, the human rights reports on Turkey simply do not reflect the truth. Particularly galling to the Greeks is the statement that "there does not appear to be any official discrimination against individuals belonging to minority groups" and that they enjoy, among other rights, "freedom of worship."

There has been a history of religious discrimination against the Greek Orthodox Church in Turkey. The best evidence can be found in the statistics: the Greek Orthodox population in Turkey has dwindled from 111,700 in 1924 to 13,500 today. A confidential diplomatic document, reporting on the oppression of Greeks in Turkey, cites these flagrant abuses:

A deliberate campaign of harassment has been reported against Greek Orthodox clerics in Istanbul, the very city where the head of the church traditionally resides. Greek religious leaders have been denied passports to travel abroad, even for pressing personal reasons. Editorials in the Turkish press have railed against the church. Following one series of articles, demonstrators laid a "black wreath on which were pinned slogans asking for the expulsion of the [Greek Orthodox] Patriarchate from Turkey."

Turkish authorities are cracking down on Greek minority schools. Teaching of the Greek language has been "severely curtailed," and Turkish officials have refused to appoint principals to Greek high schools. All repair requests in excess of \$15 were refused last year. And the Turks have begun assessing heavy taxes on Greek schools, though they are owned by charity institutions, which are supposed to be tax-exempt.

Last year, Turkish officials began "the close surveillance of persons who visit the Greek General Consulate in Istanbul" and "systematically ask for [their] identity cards." Leaders in the Greek Orthodox minority have also begun to "receive anonymous letters, threatening the property and lives of the recipients and containing demands for ransom."

There is other evidence, which we lack the

space to recount, that the State Department deliberately deceived Congress about human rights in Turkey.

Footnote: A spokesman for the Turkish embassy said his government would prefer to eschew "polemics" and discuss "issues" instead. Turkish authorities, he said, do not want to expel the Greek Orthodox Church from Istanbul, and they do not tax the church illegally. With respect to passports, the spokesman said that all Turkish citizens are limited to a single trip out of the country every two years, in order to conserve "hard currency." He also claimed that the Turkish minority in Greece is harshly treated.

RISK/BENEFIT DECISIONS AND THE PUBLIC HEALTH

HON. CLARENCE J. BROWN

OF OHIO

IN THE HOUSE OF REPRESENTATIVES

Wednesday, March 15, 1978

Mr. BROWN of Ohio. Mr. Speaker, 6 years ago, the Committee on Government Operations issued a report on the regulation of food additives, particularly nitrites and nitrates, under the Food, Drug and Cosmetic Act.

As a member of that committee, I submitted additional views relating to the arbitrary effect of the Delaney clause on the Federal Government's efforts to protect the public health and safeguard the Nation's food supply.

In those additional views, I specifically addressed myself to the need for a risk/benefit trade-off, rather than an arbitrary approach, to complex scientific and technological questions affecting our food supply. To quote briefly from the views I expressed in that August 1972 committee report:

We all want to assure that the food people eat will not harm them. And, insofar as it is possible, government should assure this. But it must be recognized that absolute guarantees may not always be possible—and for something as big, pervasive and powerful as the Federal Government—in an area where, surprisingly, so little is scientifically provable.

In view of my position on this issue, it was with considerable interest that I recently read the remarks of the chairman of the Senate Health Subcommittee on the need for a Government approach to these problems based on a realistic appraisal of the limitations of existing Federal operations in the health field.

In an address delivered February 15, 1978, at the Food and Drug Administration symposium on "Risk/Benefit Decisions and the Public Health," Senator KENNEDY made a major contribution toward moving Government policy on this issue off dead-center. Senator KENNEDY said:

We must begin educating the public to the reality that there is no such thing as absolute safety. Regulation can never completely and totally protect the public. Large segments of the American public already accept this fact. But it is time for persons in positions of leadership to strengthen this understanding with more candid discussion of the limits of regulation.

Senator KENNEDY's complete remarks delivered at this FDA symposium held at

the Air Force Academy should be read in their full context to appreciate the cogency of his call for a new approach to an increasingly urgent problem. I commend them to the attention of the Congress, the Executive, and all citizens concerned about the present and future health of the American people.

I insert the remarks of the chairman of the Senate Subcommittee on Health at this point in the Record.

REMARKS OF SENATOR EDWARD M. KENNEDY

I am pleased to be able to join you here today at this symposium on risk-benefit analysis in the area of health care. And I am especially pleased to find a distinguished group like this, under the auspices of the FDA, grappling with a subject which is of great importance to the public health and which is becoming more current and controversial with each passing year.

You have available at this conference the main ingredients for dealing with a complex issue of great public value. You have fine leadership from Don Kennedy of FDA and Doug Costle of EPA. You have a distinguished group of participating scientists and analysts. And you also have the additional ingredients of distance from Washington and the fine, cool mountain air of this outstanding setting.

With these advantages already in place, I am confident that your deliberations will help promote our understanding of more effective ways in which we can use risk/benefit analysis to improve the public health. Especially at this time of growing challenge to the traditional techniques of governmental regulation, the effective application of such analysis is essential if we are to preserve the proper balance between free competition and wise regulation in sensitive areas like health care.

I also detect a sense of urgency about this symposium that has been missing for too long in discussions of this type. I speak now as an elected official and as chairman of a Senate Subcommittee whose prime responsibility is the protection of the health of our citizens. I deal daily with the political consequences of regulation and the people it affects. I am concerned that our regulatory health authorities are growing more and more distant from the people. Our citizens no longer fully understand or trust the agencies created by Congress to protect their health. And these negative developments come at a time when the number of preventable threats to the public health is growing larger each day.

Our major challenge—yours and mine—is to enhance their strengths and eliminate the weaknesses of these agencies and their missions. Part of the challenge is to perfect the methodology of risk/benefit analysis, so that regulatory decisions of the FDA, EPA, and other agencies can more accurately reflect our public goals. The challenge also requires us to do more to educate the public about regulation and its limits, and to involve the public more directly in the regulatory process.

I need hardly remind this audience of certain facts that underlie the regulatory dilemmas we face today. We live in an expanding sea of man-made chemicals—drugs, food additives, industrial chemicals, and pesticides.

American industry manufactures 70,000 chemicals a year. One to two thousand new chemicals enter the market annually. An average auto worker is exposed each day to between 100 and 500 different chemicals.

We know that some of these substances are dangerous. Six million Americans are regularly exposed in the workplace to chemicals known to have caused cancer in animals. One million Americans have been ex-

posed to asbestos, of whom 200,000 may die of lung cancer. Approximately two million Americans are regularly exposed to benzene, which has now been demonstrated to be a very potent carcinogen.

But clearly, these cases are only the tip of the iceberg. The real or potential dangers of these myriad substances may not be known until we have much more information—whose collection may take years or even generations.

I am reminded of a story which Dr. Irving Selikoff told last spring before our Health Subcommittee. When cigarette smoking was first becoming widespread, a physician asked a distinguished cancer expert whether the practice worried him. Not at all, the expert replied. Cigarette smoking would reduce the smoking of clay pipes. And the smoking of clay pipes was known to cause cancer of the lip!

It took more than twenty years of massive experimentation with cigarettes on an unwitting American public to demonstrate that society was the loser in that trade-off. Whether we are now losing on a comparable scale on any other substances remains to be seen.

The problem is clear, but the solution is much less so. The American people have reacted by giving the Federal government a mandate to screen chemicals for hazards, and to regulate their distribution and use as drugs, food additives, or industrial chemicals.

But this is only half the answer. For we lack both the money and the manpower to test all these man-made substances for all their possible consequences. Even if we could test all these substances, available methodologies could not tell us with certainty which are dangerous to humans and which are not. And even among the dangerous compounds, we would not know precisely the magnitude of the threat.

This uncertainty is a central element in the regulatory dilemma we face. It is difficult to believe that cigarettes and asbestos are unique in their enormous adverse public effects. But which other chemicals will turn out to be the gross offenders? So far we can only speculate. There is no such thing as a simple, straight-forward answer. But we face the alarming possibility that among the enormous number of substances that our highly industrialized society is shoving into the environment are some that even now may be causing massive cancer epidemics for the current and future generations of Americans.

The dilemma is also complicated by our increasing technical ability to detect the presence of chemicals at smaller and smaller concentrations. In our present state of partial knowledge, potential dangers are everywhere, but certain dangers are rare. We are in the impossible position of walking through a minefield blindfolded, with the knowledge that the devices we trigger today may not explode for many years, or even decades.

Moreover, as science and technology advance, there are increasing numbers of products and activities that pose potential threats to the public health. Recombinant DNA is a case in point.

For the first time in history, scientists voluntarily ceased their work out of fear of potentially harmful effects of their work on public health. That issue has become a case study of the pitfalls we encounter when scientists and public officials try to work together to apply the risk/benefit calculation. In large measure, this difficulty results from dealing with a novel scientific technique whose ultimate implications are probably impossible to know at the present time.

Even when we find that risks exist, however, the federal government too often treats them inconsistently. On one hand, we subsidize tobacco-growing, and we ship tobacco abroad as foreign aid. On another hand, we

speak of banning saccharin, when medical opinion is widely split on whether it may confer potential health benefits.

And we quite appropriately restrict the use of laetrile, even for patients dying with known cancer. But we allow millions of healthy Americans to be unwittingly exposed to a pesticide like toxaphene, which clearly causes cancer in animals.

In most cases, these inconsistencies are not exclusively the fault of regulators. They also reflect the contradictory mandates and inconsistencies in regulatory law, which in turn are often the product of pressures by special interest groups that are capable of swamping the public interest. Congress has a special responsibility to review these laws to ensure they reflect the public's wishes. We cannot tolerate a situation in which inconsistent regulatory actions heighten the public's confusion and skepticism.

With all these problems, it is no surprise that America's public faith in government regulation is strained to the breaking point. Our private capacity to generate hazards to health has outstripped our public ability to evaluate and control the hazards.

One step we can take to deal with this deteriorating situation is to commit more resources to perfecting the methodology of risk/benefit analysis. In particular, we need more research aimed at improving our ability to evaluate the risks of chemicals. We must reduce the uncertainty involved in these risk assessments, and we must make these assessments cheaper and faster.

In particular, we need to devote more resources to perfecting alternatives to animal testing as a means of assessing the toxic potential of chemicals. This work goes on now at the Cancer Institute, at the FDA, at the EPA, and at the National Institute of Environmental Health Sciences. But it is research that needs better support and better coordination.

In the long term, research on risk and benefit analysis will probably prove more important than any other single step we can take to improve our capacity to protect the public health through regulation. It is work that will allow legislators and regulators to speak with much greater confidence when they warn of the hazards of a drug, a pesticide or a food additive. In this way, our research work will enhance the scientific credibility of our regulatory institutions.

But research is a long-term strategy. There are also short-term solutions that are equally important, but more difficult.

One key element is to improve the way regulatory agencies set priorities. It is clear that FDA, EPA and other regulatory institutions do not have the people or the money to carry out the huge job assigned by current law.

But it is not clear they are taking maximum advantage of the resources they now have. Our regulators need to plan better. They should publish and circulate more understandable plans and priorities for dealing with the multiple chemical threats for which they are responsible. This action will enable them to carry out their missions more effectively. And it will enable Congress and the public to deal more effectively with the isolated chemical hazards so frequently reported in the media.

Another key element in strengthening our regulatory approach is improved public education. Unfortunately, public education is often seen today as a tired and meaningless concept. It is our responsibility to give it new life and content. Public understanding of the regulatory process has always been the cornerstone of successful regulation in the past, and it will be essential for the success we hope to achieve in the future.

We must begin educating the public to the reality that there is no such thing as

olute safety. Regulation can never completely and totally protect the public. Large numbers of the American public already accept this fact. But it is time for persons in positions of leadership to strengthen this understanding with more candid discussion of the limits of regulation.

This approach does not mean we should re-open the chemical flood-gates and let Americans drift in the rising flood of toxic substances. We should give the benefit of the doubt to the public. The burden of proof could be on those who profit from the sale of chemicals to show that their distribution and use should be permitted.

But we must be honest in discussing the limits of our current resources and techniques. Risk/benefit analysis is, after all, an imperfect art. Its application will necessarily prove fallible. But the American people will accept this result and be more tolerant and supportive of regulation, as long as they understand the basis on which the decisions have been reached.

Perhaps our greatest national resource is the informed common sense of the American people. Inevitably, we shall encounter situations in which the known risks and benefits of substances are closely balanced. When these situations occur, and when citizens can control their own exposure to such substances, the correct approach is to inform the public about the nature of the risks and benefits, and to let them make their own decisions about exposing themselves to the chemicals involved.

Americans are ready for this responsibility. In fact, they are demanding it, as the lesson of the saccharin controversy now makes clear. A recent poll showed that 76 percent of Americans continue to oppose a ban on saccharin manufacture and that 77 percent of those who use it plan to keep on doing so.

By contrast, in the case of lactile, the saccharin precedent does not apply. As proposed for use in cancer treatments, lactile is a drug, and it should be held to the same strict tests of safety and effectiveness which all prescription drugs are required to meet.

We should also remember that the population using lactile is an especially sensitive group. Cancer patients are ill with a dread disease. They are much more prone to grasp at straws, and to choose a treatment without proven effectiveness, especially when the alternatives are as grim as chemotherapy or surgery or radiation. As a result, these patients are entitled to a degree of regulatory protection which the average American may not require.

Informing the public, however, does not mean printing a few lines in the Federal Register, while manufacturers fill America's living rooms with enticing advertisements for potentially hazardous products. Regulators must fight fire with fire. They must start using the print and broadcast media to inform the public in ways effective enough to make their message heard and understood.

In doing so, they must show a creativity and ingenuity they have shown too seldom in the past. They must make the esoteric concept of risk and benefit analysis understandable to ordinary citizens by using terms and images which relate to their daily lives.

This aspect of public education is essential to successful regulation in our increasingly complex modern world. By this approach, public education will become a way of involving citizens in regulatory decision-making. They will become partners in protecting themselves from potential hazards.

We must also search for other ways to promote this public partnership. In particular, we must find better ways of directly including the public in regulatory decisions.

The Environmental Protection Agency has considered experiments with public participation in its regulatory process, and the National Academy of Sciences recently made

recommendations along these lines in its study of EPA decision-making. We cannot overestimate the importance of public participation in regulation.

It is increasingly clear to the average American that there is a large dose of subjective judgment in the rules which pour out of EPA, FDA, OSHA and other regulatory agencies. Even under the best circumstances, this subjectivity is inevitable. It reflects the limits of risk/benefit analysis and the realities of politics. It is nothing to apologize about.

But if decisions are subjective, then the process by which these decisions are made becomes of great importance. That process will not be accepted as legitimate unless it is open and understandable. And the way to make it open and understandable is to ensure that representatives of the public have direct access to it.

Regulation has become one of the foundations of modern public health in the United States. The legitimacy and strength of FDA and EPA and other regulatory institutions are national health resources. They deserve far greater emphasis and attention by Congress and the public than they have received in recent years. I look forward to the recommendations and suggestions of this symposium as a useful step in meeting the growing challenge. And I also look forward to working with you, as we build a wiser and more effective future for our nation's system of public health.®

THE 13TH ANNIVERSARY OF HUNGARIAN INDEPENDENCE

HON. JOHN G. FARY

OF ILLINOIS

IN THE HOUSE OF REPRESENTATIVES

Wednesday, March 15, 1978

® Mr. FARY. Mr. Speaker, today marks the 130th anniversary of the Hungarian Revolution of 1848, in which the people of Hungary rose up against the domination of the Hapsburg Empire. Early in March of that year, the great patriot leader, Louis Kossuth led the national demand for parliamentary government. Just a year before, national elections had supported the movement for autonomy, culminating the famous ten points, including responsible government, popular representation, religious liberty, abolition of serfdom, equality before the law and other principles basic to a free society. These were adopted by the deputies of the Hungarian diet on March 15, 1848, and they thereby became equivalent to a constitution.

Tragically, the new government was to be ruthlessly suppressed by invading armies, which occupied Budapest in January of 1849. Resisting to the bitter end in the face of overwhelming odds, the Hungarian diet proclaimed a republic in April, electing Kossuth as "governor-president." The republic collapsed under the combined assault of Austrian and Russian troops, but Kossuth escaped.

Nevertheless, the people's will for freedom lived on, and in 1867, only 16 years after the uprising, the constitution of 1848 was restored peacefully and Hungary acquired responsible government. After the First World War, the political union with the Hapsburg dynasty ended, and Hungary became a wholly independent nation.

In celebrating Hungarian Independence Day, we honor the courage and vision of those who led their people's struggle for national freedom in the last century. More than that, we remember that spirit of patriotism which sustained Hungarians in every age and which has flourished in our own time. The memories of the Hungarian Revolution in 1956 are still fresh and vivid in the hearts and minds of Hungarians, which is testimony to their acute desire for real independence.

The Revolution of 1848, even as that of 1956, aroused great sympathy in the United States. Kossuth's visit in 1851 was a dramatic occasion for celebrating American support for Hungarian freedom. Since that time countless thousands of Hungarians have come to America, seeking larger liberties. Today, there are well over a million Hungarian-Americans, whose contributions to our national life are outstanding in every area of endeavor including science and industry, music and the arts, journalism and entertainment.

Mr. Speaker, on this special day I join with our fellow Americans of Hungarian descent in celebrating the independence that the great patriot, Louis Kossuth, helped establish. However, it should not go unnoticed that the same Russian imperialism that prevailed in 1849 is still present today and continues to oppress the legitimate aspirations of the Hungarian people for real independence and to be free of foreign domination. Let us pray that those noble aspirations are realized one day soon.®

HEARINGS BY THE HOUSE SELECT COMMITTEE ON AGING, DELAWARE COUNTY, PA.

HON. ROBERT W. EDGAR

OF PENNSYLVANIA

IN THE HOUSE OF REPRESENTATIVES

Wednesday, March 15, 1978

® Mr. EDGAR. Mr. Speaker, on Friday, March 3, the Select Committee on Aging, represented by Congressmen Mike Blouin and Dave Evans, held field hearings in my district to gather testimony regarding the Older Americans Act. I participated in these hearings which, in my view, were quite productive. For the past few days I have inserted into the Record portions of the testimony we received. The ninth section follows:

BUNTING FRIENDSHIP FREEDOM HOUSE, INC.,
Darby, Pa.

THE HOUSE SELECT COMMITTEE ON AGING

The Bunting Friendship Freedom House, Inc., would like to go on record as stating that the Government is to be complimented for at least recognizing the plight of its older Americans. We think it has been a long time coming and even now, we have only scratched the surface. Even though we are providing health screening, socialization, recreation, nutritious meals, nutrition information and lawyers for the writing of wills for some people, how about the thousands we are not reaching; some who are stored away in nursing and/or boarding homes, unfit for human habitation? There should be some mecha-