
Item ID Number 01188

Author Bababunmi, Eritan A.

Corporate Author

Report/Article Title Toxins and Carcinogens in the Environment: An Observation in the Tropics

Journal/Book Title Journal of Toxicology and Environmental Health

Year 1978

Month/Day

Color

Number of Images 9

Description Notes Alvin L. Young filed this item under the category "DDT/Human Toxicology and Environmental Fate"

TOXINS AND CARCINOGENS IN THE ENVIRONMENT: AN OBSERVATION IN THE TROPICS

Enitan A. Bababunmi

Department of Biochemistry, School of Medicine,
University of Ibadan, Ibadan, Nigeria

The incidence of primary liver cancer in the countries of tropical Africa is the highest in the world. There is a growing belief that the relatively high prevalence of hepatocellular carcinoma in Nigeria may have a multiple chemical factor etiology in such forms as food contaminants, herbal teas, and environmental chemicals. Major chemical toxins and carcinogens that have been identified so far in the tropical environment include supotoxin, cycasin, mushroom toxin, capsaicin, oxalic acid, prussic acid, fluorooleic acid, N-nitroso compounds, aflatoxin, palmotoxin, pyrrolizidine alkaloids, quinine, DDT, and cyclamate.

INTRODUCTION

During the past two decades, there has been an increasing awareness of the hazards to human and animal health from various chemical substances that occur in the tropical environment. There is evidence to indicate that various health problems, including some forms of cancer, have their origin in the presence of toxic chemicals in medicines, herbal residues, pesticides, foods, and drinks. Some of these problems are common to countries throughout the world, while others are peculiar to Africans who live in the tropics. For example, altogether the incidence of primary liver cancer in adult males is the highest in the world in African countries such as Nigeria, Uganda, and Mozambique (IARC, 1971).

The primary objective of the present review is to focus attention on the presence of toxic chemicals in foods and in the environment of tropical African countries, particularly Nigeria, which is the most populous country in Africa. Some of these toxins have been shown to possess carcinogenic (or mutagenic) properties in various biological systems. However, in a large number of cases, adverse effects of some of these toxic substances on human health are not known. It is hoped that this paper will have the important effects of stimulating more research into the special toxicological problems that are of concern to people living in the tropics.

This article was written during the author's tenure as an ICRETT Fellow of UICC (1977) at the Department of Biochemistry and King's College, University of Cambridge, Cambridge, England.

Requests for reprints should be sent to Enitan A. Bababunmi, Department of Biochemistry, School of Medicine, University of Ibadan, Ibadan, Nigeria.

ENDOGENOUS FOOD TOXINS

Endogenous food toxicity is widespread in tropical Africa. Nicholls et al. (1961) dealt with the various types of tropical foods that carry toxins. The review of Crampton and Charlesworth (1975) adequately covers the occurrence of food toxins in the nontropical world.

Hypoglycin

This toxin is contained in the unripe fruit of the food plant, *Blighia sapida*. In Nigeria the fruit is called isin, whereas it is commonly known as akee in Jamaica. There are two types of this toxin, A and B. Although both types are biologically active, the A type (β -methylenecyclopropyl-alanine) is the more toxic. Very little work has been done on the chemistry and the biological function of the B type.

Dioscorine

This toxic chemical is sometimes referred to simply as dioscorea toxin; it is an alkaloid that is present in *Dioscorea hispida*. The main toxic species of these tropical yams of West Africa are *D. hispida*, *D. dumetorum*, *D. sansibarensis*, and *D. bulbifera*. Since the isolation and identification of the related alkaloid dehydrodioscorine by Bevan and Hirst (1958), scientists have not looked into the existence of these or other structures in the other species of the wild yams.

Sapotoxin

Some tropical foodstuffs such as soybean, breadfruit, tomato, melon, orange, and groundnut contain some sapotoxin, which, at high concentrations, has drastic effects on humans. The toxin can cause gastroenteritis and produce paralysis of the nerve centers. Sapotoxin is a nitrogen-free glycoside.

Cycasin

Cycasin occurs in plants of the family Cycadaceae, which are indigenous to tropical and subtropical regions (IARC, 1972). The biologically active moiety of cycasin is the aglycone methylazoxymethanol. Cycad seeds are used as medicine in some parts of Africa, Indochina, and India. Feeding of a cycad diet has been shown to induce malignant tumors of the liver in the rat, mouse, hamster, fish, and guinea pig (IARC, 1972).

Mushroom Toxin

A large number of mushroom species are edible, but certain species that are eaten in the tropics are poisonous. Examples of toxins elaborated by these species are agaritine (*Agaricus bisporus* toxin) and champignon (*A. hortensis* toxin). Muscarine and *Amanita phalloides* toxin have been reported to be toxic by Nicholls et al. (1961).

Names for different species of mushrooms are descriptive in many parts of the tropics. In the western state of Nigeria, these names give an indication either of the habitat, morphology, and texture or of the growth habitat of the fungi (Oso, 1975). *Corprinus ephemerus*, a fungus that grows on dunghills, appears at night or early in the morning, and within a very short time the pileus is fully expanded. However, it deliquesces in the sun. It is considered poisonous by the Yoruba people of Nigeria, and local doctors use it in the preparation of some charms. Extracts of the fungus should be tested for mutagenicity.

Capsaicin (Red Pepper Toxin)

The substance is the active principle of the plants *Capsicum annum* and *C. frutescens*. It is a powerful irritant and a skin blister. Although these plants are rich in vitamin C, excessive feeding on them can be dangerous. Species of pepper such as *Piper nigrum* contain alkaloids and volatile oils that are toxic to both animals and humans.

Halogeton Toxin (Oxalic Acid)

Plant species such as *Halogeton glomeritus*, *Celosia argentea*, *Amaranthus candatus*, *Celosia laxa*, and *Talinum* are used as food in tropical Africa, especially on the west coast. These vegetables contain significant levels of oxalic acid (Oke, 1967). There are conflicting data on the lethal dose for humans. However, Oke showed that an average healthy Nigerian would consume about 6 g of oxalic acid daily, on the basis that 50 g of fresh vegetables could be consumed at a meal.

Cyanogen (Prussic Acid)

Tropical plants, cassava, maize, and sugar cane are good sources of cyanogenetic glycosides such as linamarin and dhurrin. Cassava (manioc; *Manihot utilissima*) is the most widely grown of all tropical root crops. It is mainly a carbohydrate food with a very low protein content. In West Africa, manioc flour (gari) has become a major diet. In the West Indies the dried flour is called farina. All over the tropics it is used as food for the young and adults in one form or another.

The enzyme linase liberates prussic acid (HCN) from linamarin. HCN is toxic to many species of animals, including humans. The production of HCN varies with the variety of the plant and the conditions of cultivation (Osuntokun et al., 1969).

Although significant amounts of HCN are said to occur only in the bitter variety of cassava, there is in fact no clear differentiation between the sweet and bitter strains. The fact that the cortex of the root contains the highest concentrations of the toxin provides biological protection for the plant against invading insects. Chronic cyanide intoxication by laboratory animals has resulted in neural damage in the guinea pig, rabbit, sheep, and cat.

Fluorooleic Acid

The seeds of the West African plant *Dichapetalum toxicarium* contain fluorooleic acid and some minute amounts of shorter-chained fluoro acids. These fluoro compounds are toxic. Local doctors in the countries of West Africa often administer the seed extracts in an attempt to produce loss of motor activity, loss of sensation, and sometimes death (Peters et al., 1960). Free oleic acid uncouples oxidative phosphorylation (Pressman and Lardy, 1956).

N-Nitroso Compounds

Dimethylnitrosamine (DMN) and diethylnitrosamine (DEN) have been detected in measurable quantities in several alcoholic beverages in Nigeria (Joaquim, 1973). Bababunmi et al. (1977) reviewed the extent of contamination of these drinks by the two carcinogens. There is some evidence that the formation of these nitrosamines involves bacterial action.

FUNGAL TOXIC CONTAMINANTS

Fungus-infected foodstuffs are the cause of many types of food poisoning (see Kadis et al., 1972). In the tropics, a variety of fungal species have been reported to be involved in some toxicity syndromes. Notable examples are *Aspergillus*, *Penicillium*, *Stachybotrys*, *Trichoderma*, *Fusarium*, *Pseudomonas*, and *Helminthosporium* species. The most ubiquitous in Nigeria are *Aspergillus* and *Penicillium*. Many strains of each of these fungi are toxigenic. Among the common toxic metabolites of the aspergilli are aspergillie acid, flavacol, β -nitropropionic acid, kojic acid, sterigmatocystin, ochratoxin, aspertoxin, aflatoxin, and palmotoxin. *Penicillium* elaborates the mycotoxins patulin, islanditoxin, luteoskyrin, rugulosin, citrinin, frequentic acid (citreomycetin), gliotoxin, costaclavine, and citreoviridin. Of these, aflatoxin has been studied most extensively, mainly because of its potent carcinogenic properties. A cometabolite of aflatoxin, palmotoxin, has been the subject of investigation for some years in this laboratory. Many other naturally occurring toxins (Table 1) that are known should be tested for carcinogenicity.

Aflatoxin

The literature on the biochemistry, toxicity, carcinogenicity, and mutagenicity of aflatoxin is enormous (Goldblatt, 1969; Wogan, 1975a, 1975b; IRAC, 1976). The discovery of aflatoxin in the tropics (Asplin and Carnaghan, 1961) as a contaminant of human and animal foodstuffs (groundnuts) aroused the interest of scientists all over the world because of its health hazards and possible economic effects on the producers of these foods. Nigeria is one of the world's major exporters of groundnuts. Other tropical foods that are vectors of aflatoxin are beans, corn, rice, cocoa, and wheat.

TABLE 1. Some Known Naturally Occurring Toxins

Toxic substance	Occurrence in	Possible human exposure through
Fusaric acid	<i>Fusarium oxysporium</i>	Tomato, sorghum, maize
Periconin	<i>Periconia circinata</i>	Sorghum
T toxin	<i>Helminthosporium maydis</i>	Maize
Helminthosporoside	<i>Helminthosporium sacchari</i>	Sugarcane
Tabtoxin	<i>Pseudomonas coronatuciens</i>	Tobacco
Javanicin	<i>Fusarium solani</i>	Maize

Aspergillus flavus, the main source of aflatoxin, is common in air and soil. It will grow on agricultural products and food materials in a favorable environment with a relative humidity of 70-90% and a minimum temperature of about 10°C. In general, the growth of *A. flavus* can be correlated with the production of aflatoxin except at high temperatures, 40-50°C.

In different regions of Muranga in Kenya (East Africa), mean aflatoxin levels of about 0.25 ppm in food and 0.1 mg/l in beer have been detected (IARC, 1972). When common food preparations of Nigeria's principal food crops were sampled from local market stalls and assessed for aflatoxin contamination by conventional techniques, the aflatoxin content was not less than 0.5 ppm in any of the foods (Bababunmi, 1976). Several industrialized countries such as the United States, Denmark, Britain, and Italy consider a level of aflatoxin of the order of 0.25 ppm as dangerous and the contaminated food as unconsumable.

Although the proportional contribution of agriculture to the Nigerian economy continues to fall, it will continue to be the single most important sector in the economy for a long time (Aboyade, 1971). The export value of cocoa ranks second to that of oil in Nigeria. In 1974, Nigeria's foreign trade was \$3.462 billion. If oil accounted for 80% of the export value in the 1974-1975 fiscal year, other export products such as cocoa, groundnuts, and palm products should account for about \$700 million. Therefore, if aflatoxin contamination in this class of export commodities is not eliminated, Nigeria's foreign reserves may diminish continuously.

Palmotoxin

Isolation of two additional fluorescent toxins from cultures of *A. flavus* on unfermented palm sap (a common West African wine) obtained from a variety of *Elaeis guineensis* was reported by Bassir and Adekunle (1968). Toxicity titrations of palmotoxins B₀ and G₀ on 6-d-old White Rock chick embryos indicated that B₀ is as toxic as aflatoxin B₁. Recent results of Uwaifo et al. (1977) suggest that the structures of the palmotoxins could be heterocyclic and may be similar to those of the aflatoxin family (Asao et al., 1965). Comparative mutagenicity studies by

Uwaifo et al. (1978) show that palmotoxin B₀ induces microlesions that consist of point mutations in Ames' tester strains of *Salmonella typhimurium*. However, the ratio of the mutagenicity of aflatoxin B₁ to that of palmotoxin B₀ is about 6:1.

In Nigeria and several developing African countries, several facilities and preservation techniques for agricultural products are quite inadequate. The combination of this unfortunate situation, the natural warm and moist weather, a dirty environment, human error, and ignorance is conducive to the growth of *A. flavus* and consequently to the elaboration of mycotoxins (such as aflatoxin and palmotoxin) on agricultural commodities. It seems to me, therefore, that the problems associated with mycotoxin contamination of food and agricultural products will remain in the developing tropical regions of the world for some time, at least in the foreseeable future, unless very drastic control measures are initiated.

HERBAL RESIDUES

For years, herbalists and local doctors in tropical Africa have used herbs and their concoctions to treat various human diseases (Dalziel, 1948). In modern times, countries such as Nigeria and Ghana have intensified their search for authentic medicinal plants and their active principles. Apart from their use as local medicines, many toxic plant species are used as food in many parts of West Africa.

Many chemical compounds have been isolated from useful plants of West Africa and characterized in their pure forms. In this respect, scientists in the Department of Chemistry of the University of Ibadan have contributed immensely to the knowledge of the chemistry of active principles in plants. Toxicological and other biological studies of these chemicals are, however, scanty. Miller and Miller (1976) stated that the plant genera *Crotalaria*, *Senecio*, *Laburnum*, and *Heliotropium* have long been known to contain carcinogenic substances (IARC, 1976), some of which are pyrrolizidine alkaloids.

FOREIGN TOXIC CHEMICALS

Environmental toxins of this class exist in such forms as medicines, pesticides, and food additives. With the gradual emergence of some tropical African countries (for example, Nigeria) from the underdeveloped to the developing state, environmental pollution and the presence of industrial materials such as those used in the processing and packaging of foods are potential sources of toxins. Common examples in this category are ionizing radiation, plasticizers, adhesives, paraffins, printing inks, and treated papers. Well-recognized environmental toxic (or carcinogenic) chemical substances in this tropical area of the world include quinine (antimalarial drug), DDT (insecticide), and cyclamate (food additive).

Quinine

Malaria is a disease that occurs throughout the tropical and subtropical countries. It is actually a group of diseases characterized by recurrent attacks of fever, anemia, and enlargement of the spleen. Malaria can also occur in temperate climates if the environmental temperature is right for the protozoan species (e.g., *Plasmodium falciparum*) to complete their life cycle in the female *Anopheles* mosquitoes. The parasite lives in the red blood cells. There are three forms of the malaria parasite in humans corresponding to malignant tertian, benign tertian, and quartan malaria. In the tropics the most common malaria is the malignant tertian, although the other two varieties have been identified in a very few cases.

Chloroquine, mepacrine, and quinine are drugs that are very effective in rapidly destroying the parasite in the blood. Chloroquine (Nivaquine) is the most widely used antimalarial drug and has been reported to be the safest. Mepacrine (Atebrin) can be given only intramuscularly and is not often used.

Quinine is the oldest of all the antimalarial medicines. It is also the quickest acting. For many years quinine was the only drug available for the treatment of malaria. Although quinine has some toxic side effects, it is still used, especially for cases that are resistant to other drugs. Quinine was the first alkaloid isolated from the bark of the *Cinchona* tree. A single oral dose of about 8 g is regarded as fatal for an adult man. Quinine poisoning usually results in nausea, headache, visual disturbances, nervous system and cardiovascular system disorders, and respiratory arrest.

DDT

The insecticidal properties of DDT are well known (IARC, 1974). This compound has been extensively used as an insecticide and produced commercially for this purpose since 1943, when a low-cost production technique was developed. It has been widely used for the control of numerous insect pests—for example, as a mosquito larvicide and as a residual spray for eradicating malaria in the tropics. DDT is distributed by the World Health Organization throughout the world for the prevention of yellow fever, sleeping sickness, and malaria. Apart from these uses, quantities of DDT are used for the treatment of peppers, onions, soybeans, groundnuts, cowpeas, and sweet potatoes, in storage.

Tropical countries such as the Upper Volta and Ghana use at least 500 kg of DDT annually for agricultural purposes. In 1973, research on the environmental effects of pesticides in the tropics was carried out at the International Institute for Tropical Agriculture (IITA), Ibadan. The study was concerned with the effects of DDT (used as a crop protector) on the fertility of agricultural soil. Cowpea (*Vigna unguiculata* var. Prima), which is a high-yielding legume, was selected in the IITA study because it requires regular pesticide applications and also because of its growing

importance in tropical agriculture. Since 1970, DDT has been restricted to uses other than on human and animal foodstuffs in the more advanced countries. The hepatocarcinogenicity of DDT on oral administration has been amply demonstrated in several strains of mice. Liver cell tumors were produced in both male and female mice, and an increased tumor incidence was reported in some other organs. The most frequent tumor types were leukemia, reticulum cell sarcoma, carcinoma of the lungs, and hemangio-endothelioma (IARC, 1974).

Cyclamate

Calcium cyclamate (cyclohexylsulfamic acid calcium salt) is still used as a nonnutritive sweetener in a large number of soft drinks in many African countries. The use of cyclamic acid as a sweetener has been banned in several industrialized countries because the compound was suspected of being a bladder carcinogen in the rat.

CONCLUSION

Apart from foods, beverages, and medicines, there are other sources of potential toxins and carcinogens that are introduced by humans into the tropical environment, especially in the cities, in such forms as narcotics and atmospheric pollutants. With the arrival of various industries in big African cities, inhalation of dust, vapors, and exhausts presents a new form of danger. Epidemiologic appraisal of these factors is lacking. There is a need to estimate the total load of toxins and carcinogens in the tropical environment.

REFERENCES

- Aboyade, O. 1971. Nigeria's economy. In *Africa South of the Sahara*, 1st ed., pp. 558-563. London: Europa.
- Asao, T., Buchi, G., Abdel-Kader, M. M., Chang, S. B., Wick, E. L., and Wogan, G. N. 1965. The structures of aflatoxins B and G₁. *J. Am. Chem. Soc.* 87:882-886.
- Asplin, F. D. and Carnaghan, R. B. A. 1961. The toxicity of certain groundnut meals for poultry with special reference to their effect on ducklings and chickens. *Vel. Rec.* 73:1215-1219.
- Bababunmi, E. A. 1976. Excretion of aflatoxin in the urine of normal individuals and patients with liver diseases in Ibadan (Nigeria). In *Detection and Prevention of Cancer*, ed. H. E. Nieburgs. New York: Deker.
- Bababunmi, E. A., Uwaifo, A. O., and Bassir, O. 1977. Hepatocarcinogens in Nigerian foodstuffs. *World Rev. Nutr. Diet* 28: article 44.
- Bassir, O. and Adekunle, A. A. 1968. Two new metabolites of *Aspergillus Flavus* (Link). *FEBS Lett.* 2:23-25.
- Bevan, C. W. L. and Hirst, J. 1958. A convulsant alkaloid of *Dioscorea dumetorum*. *Chem. Ind.* 4: 103.
- Crampton, R. F. and Charlesworth, F. A. 1975. Occurrence of natural toxins in food. *Br. Med. B II.* 31:209-213.
- Dalziel, J. M. 1948. Useful plants of west tropical Africa. In *Flora of West Tropical Africa*, eds. J. Hutchinson and J. M. Dalziel. London: Crown Agents for the Colonies.

- Goldblatt, L. A. 1969. *Aflatoxin*. New York: Academic Press.
- IARC. 1971. *Liver Cancer*. Sci. Publ. no. 1. Lyon: International Agency for Research on Cancer.
- IARC. 1972. *Evaluation of Carcinogenic Risk of Chemicals to Man*, vol. 1. Lyon: International Agency for Research on Cancer.
- IARC. 1974. *Chemical Carcinogenesis Essays*. Sci. Publ. no. 10. Lyon: International Agency for Research on Cancer.
- IARC. 1976. *Evaluation of Carcinogenic Risk of Chemicals to Man*, vol. 10. Lyon: International Agency for Research on Cancer.
- Joaquim, K. 1973. Nitrosamine contamination of some Nigerian beverages. Ph.D. thesis, Ibadan University.
- Kadis, S., Ciegler, A., and Ajl, S. J. 1972. In *Microbial Toxins: A Comprehensive Treatise*, vol. 8, *Fungal Toxins*. New York: Academic Press.
- Miller, J. A. and Miller, E. C. 1976. Carcinogens occurring naturally in foods. *Fed. Proc.* 35:1316-1321.
- Nicholls, L., Sinclair, H. M., and Jelliffe, D. B. 1961. *Tropical Nutrition and Dietetics*. London: Bailliere, Tindall & Cox.
- Oke, O. L. 1967. Oxalic acid in plants and in nutrition. *World Rev. Nutr. Diet.* 8:262-303.
- Oso, B. A. 1975. Mushrooms and the Yoruba people of Nigeria. *Mycologia* 67:311-319.
- Osuntokun, B. O., Monekosso, G. L., and Wilson, J. 1969. Cassava diet and a chronic degenerative neuropathy. An epidemiological study. *Niger. J. Sci.* 3:3-15.
- Peters, R. A., Hall, R. J., Ward, P. F. V., and Sheppard, N. 1960. The chemical nature of the toxic compounds containing fluorine in the seeds of *Dichapetalum toxicarium*. *Biochem. J.* 77:17-23.
- Pressman, B. C. and Lardy, H. A. 1956. Effect of surface active agents on the latent ATP-ase of mitochondria. *Biochim. Biophys. Acta* 21:458-466.
- Uwaifo, A. O., Emerole, G. O., and Bassir, O. 1977. Comparative study of the fluorescent characteristics of solutions of aflatoxins and palmotoxins in chloroform. *J. Agric. Food Chem.* 25:1218-1220.
- Uwaifo, A. O., Emerole, G. O., Bababunmi, E. A., and Bassir, O. 1978. Comparative mutagenicity of palmotoxin B₀ and aflatoxin B₁. In press.
- Wogan, G. N. 1975a. Mycotoxins. *Annu. Rev. Pharmacol.* 15:437-451.
- Wogan, G. N. 1975b. Dietary factors and special epidemiological situations of liver cancer in Thailand and Africa. *Cancer Res.* 35:3499-3502.

Received March 12, 1978

Accepted April 3, 1978