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Journey from food toxins to food safety: Transition over a century in service of nation

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Since the first report of lathyrism in 1926, the ICMR-National Institute of Nutrition (NIN) at Hyderabad, India, has made tremendous contributions in the field of food toxins/food safety for the benefit of the people. The present article highlights the Institute's work on various food toxins/foodborne diseases since its inception and discusses the important contributions made in the context of public health protection that formed the basis for several national policies on their prevention and control. The investigations on food toxins, in the initial decades, were limited to the description of lathyrism and its endemicity. Subsequently, the horizon was broadened to include the problem of mycotoxins and mycotoxicosis, which had received global attention and variety of other disease outbreaks investigations leading to total food safety transition in the forthcoming decades. Important contributions in epidemiological investigations, reproduction of the disease in experimental animals, surveillance and monitoring studies, development of methods for detection of food toxins and contaminants, evolving strategies for prevention and control and developing the concept of risk assessment and risk management for addressing food safety issues in the country are discussed.

Key words Disease outbreaks - food contaminants - food safety - food toxins - lathyrism - mycotoxins

Introduction

Food safety is essential for good health and protection against foodborne illnesses that result from consumption of food contaminated with various food toxins and toxic microorganisms. Food safety has assumed considerable health significance and economic implications in recent years. In the past few decades, global attention has shifted from food toxins towards ensuring safety of food produced, traded and consumed. The contributions of ICMR-National Institute of Nutrition (NIN), Hyderabad, India, in the field of food toxins and food safety need to be viewed from this perspective having societal objectives ultimately benefiting people.

Research on food toxins at the NIN has spanned over several decades beginning from 1926 under Sir Robert McCarrison, the first Director of the Institute¹. The investigations in the initial decades at the Institute were limited to the description of lathyrism and their endemicity. Subsequently, the investigations were broadened to include problem of mycotoxins and mycotoxicosis and variety of other disease outbreaks/investigations leading to total food safety. The present article highlights the work of NIN on various foodborne diseases since inception and the transition from food toxins and disease outbreaks to food safety.

Investigations on food toxins: A chronology

The chronology of investigations on food toxins and the gradual transition to broader studies relating to food safety can be viewed in four phases based on the studies published during each phase as described in the Table. The number of published papers as accessed from the NIN's list of publications catalogued in the NIN library from 1926 to 2017 and distributed under each decade is shown in the Figure. The first phase spanning the period of 37 years from 1926 to 1963 was largely devoted to study of lathyrism and to some extent edible oils. The second phase spanning 16 years from 1964 to 1980 was dominated by investigations on aflatoxins following its discovery in 1960. This phase is characterized by investigations of several disease outbreaks due to naturally occurring food toxins. Studies were also

initiated on nutritional and toxicological evaluation of unconventional sources of oils. The experience with food toxins and their significance to public health and also the developments in the international arena prompted to shift emphasis from food toxins to

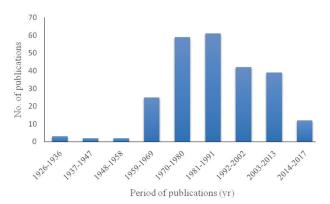


Figure. Number of published papers on food toxins and disease outbreaks during 1926-2017. *Source*: List of publications of ICMR-National Institute of Nutrition, Hyderabad from NIN library.

Table. Chronology of investigations on food toxins at ICMR-National Institute of Nutrition since its inception		
Phase	Number of years	Study focus and contributions
1 (1926-1963)	37	Lathyrism: Epidemiology, identification and isolation of toxic factor, reproduction of disease in experimental animals, methods of removal of toxic factor, adulteration issues
2 (1964-1980)	16	Aflatoxin: Biological effects in experimental animals, natural occurrence in groundnut, acute aflatoxicosis outbreak in human populations Ergot alkaloids poisoning in man Epidemic dropsy Disease outbreaks from adventitious contamination of food crops Toxins in edible oils Nutritional and toxicological evaluation of unconventional oils
3 (1981-2000)	19	 Food safety for public health protection using risk-based approaches Evolving national strategies for food safety assurance and control Food contaminants monitoring programmes Capacity building/training in analytical methodology of food toxins/contaminants Foodborne diseases due to mycotoxins, bacterial pathogens, aquatic biotoxins, chemical toxicants, food adulterants Safety assessment of damaged/discoloured food grains Risk assessment of food contaminant exposure
2001-present	16	 Food safety - newer issues Food safety assessment of genetically engineered foods Investigation on fungal and aflatoxin contamination of discoloured and stored rice for public distribution Information, exchange and communication strategies for ensuring food safety - KAP studies on foodborne pathogens Food contaminants and hazards in processed foods and exposure assessment: Mycotoxins in processed RTE groundnut snacks, RTE spice mixtures and botanicals Monitoring of pesticide residues in food and water and estimating human exposure
RTE, ready to eat; KAP, knowledge attitude and practices Source: List of publications of ICMR-National Institute of Nutrition, Hyderabad from NIN library		

food safety. In this phase spanning 19 years, the focus of investigations was gradually broadened to bring in food safety issues from the perspective of protection of public health and using internationally proposed risk-based approaches. In addition, important food safety issues were addressed from a national perspective by identifying food safety problems, infrastructure requirements and laying down the criteria to formulate national policies relating to food safety assurance and control. The work on food toxins and food safety carried out in the earlier phases has been continued in the fourth phase with a focus on newer areas of food safety assessments such as that of novel foods using specific procedures outlined by international fora and adapted to Indian context and investigations on microbial pathogens, mycotoxin exposure assessment and pesticide residues in food and water. It is significant to note that the majority of studies, mostly on mycotoxins were published during 1970-1991 (Figure).

This article describes significant contributions of the NIN in the field of food toxins and food safety with respect to investigation of specific foodborne diseases including identification and isolation of the toxic factors responsible and reproduction of the disease in experimental animals, surveillance and monitoring studies and strategies developed for prevention and control, and food safety initiatives developed for public health protection at the national level.

Investigation of specific foodborne diseases

Investigation on lathyrism

The work on food toxins at the institute during the first two decades (1926-1946) was devoted to investigations on lathyrism. Lathyrism constituted a major public health problem in several parts of Central India, and the occurrence of the disease in epidemic form was reported^{2,3}. Various investigators suspected the association between lathyrism and long-term consumption of the pulse *Lathyrus sativus* and the increase in the number of cases during famine conditions^{2,3}.

The chronology of events and important data that emerged from the Nutritional Research Laboratories (later named as NIN) were as follows (*i*) an understanding of the food system in the endemic regions and the social, economic and agriculture aspects that compelled the people to consume *L. sativus* pulse as a dietary staple, (*ii*) investigations into the nature of the disease and presenting symptoms, (*iii*) efforts leading to identification of the presence of neurotoxic principle that caused the disease, (iv) significant breakthroughs in creating chick as an animal model for finding toxicity of L. sativus, (v) successful demonstration of removal of toxic factor from L. sativus pulse using simple household measures, and (vi) the identification of emerging dimensions of the lathyrus problem regarding the adulteration of pulses with L. sativus and alerting the governments to take appropriate measures to prevent the use of L. sativus pulse including recommendation on a ban on its sale under the then Prevention of Food Adulteration Act in 1961⁴ which is still in force under the new Food Safety and Standards of India Act 2011⁵. Recent investigations indicated that the decline in consumption and prevalence of lathyrism cases in regions where they were earlier observed⁶.

Investigation on mycotoxins

The Institute has made significant contributions in the field of mycotoxins particularly aflatoxins. Aflatoxins discovered in 1960 in a feed ingredient of groundnut meal have been recognized as the most potent hepatotoxic and carcinogenic metabolites of Aspergillus flavus and A. parasiticus⁷. The work contributed substantially to the understanding of the nature and toxicity of aflatoxins. Work on aflatoxins was initiated during 1963, and intensive work was carried out until the late 1970s. The most significant contributions during this period have been in (i) demonstrating the biological effects including toxicity and carcinogenicity in experimental animals including monkeys, (ii) demonstrating malnourished (protein /vitamin deficient) animals as more susceptible to aflatoxin toxicity than well-nourished animals, (iii) describing aflatoxicosis disease outbreaks in human populations in Western India in 1974 due to consumption of rain-affected mould damaged maize, (iv) assessing the potential of contamination in various agricultural commodities of dietary significance as well as export-oriented commodities such as groundnut and spices, (v) identifying possibility of using genetic approaches for developing aflatoxin-resistant groundnut and other crop varieties, (vi) identifying inhibitory action of certain chemical constituents present in spices such as black pepper, and (vii) identifying methods for removal from and reduction of aflatoxins in foods during household cooking procedures^{7,8}. Recognizing the significant contributions of the Institute towards food toxins and disease outbreaks investigation particularly of aflatoxins during the mid 1960s and 1970s, the Indian Council of Medical Research (ICMR)

established the Food and Drug Toxicology Research Centre in Hyderabad in 1978⁹.

Investigation on outbreaks of mycotoxicosis in human populations

The Institute has made significant contributions to the nature and understanding of mycotoxicosis disease occurrence in humans. Until now four major acute mycotoxicoses are known in the world and all these four were described from India by the NIN: (i) Described acute aflatoxin hepatitis in Banswada and Panchamahals districts of Rajasthan and Gujarat during 1974-1975 affecting 400 people with a mortality of 100 due to consumption of aflatoxin-contaminated maize¹⁰. The pioneering work was the first report directly incriminating aflatoxin in food as human health hazard at the community level and gained wide international recognition and acceptance of aflatoxin induced toxicity in humans through contaminated staple cereals. (ii) Investigated outbreak of enteroergotism that occurred in Jaipur and Sikar districts of Rajasthan during 1975 due to the consumption of pearl millet contaminated with Clavine group of alkaloids¹¹. Epidemiological investigations led to the derivation of non-toxic level of ergot alkaloids of 28 µg/kg body weight from intake of 200 g of pearl millet¹¹. It was named Enteroergotism, different from the classical vascular ergotism ravaging Europe in medieval years due to classical ergot alkaloids of the rye¹². (iii) Studied the outbreak that occurred in the Kashmir Valley during 1987 affecting over 50,000 persons due to the consumption of wheat and wheat products and attributed it to trichothecene group of mycotoxins, especially the deoxynivalenol¹³. The investigation helped in deriving a tolerance level for deoxynivalenol of 34 µg/kg for wheat and wheat products consumed in India. (iv) Attributed the outbreak that occurred during 1996 in the region of Deccan Plateau affecting 1424 people as due to the consumption of fumonisin-contaminated sorghum and maize¹⁴. An important finding revealed by this investigation was the potential for the occurrence of high levels of fumonisins in sorghum that could result in human diseases.

Monitoring of various food commodities for contamination with aflatoxin & other mycotoxins

The Institute has contributed significantly to the understanding of the nature and extent of mycotoxin contamination in oilseeds chiefly groundnut, cereals/millets and spices and the level of risk associated with the mycotoxin exposure from these. Initially, focus of monitoring was on groundnut, and studies included nature and extent of the aflatoxin problem in groundnut, the critical factors influencing its contamination particularly seasonal variation, period and type of storage after harvesting, role of factors that favour aflatoxin production particularly trace elements and varietal differences in level of contamination¹⁵. A significant finding was the identification of an aflatoxin-resistant groundnut variety US-26¹⁶ which laid foundation for future studies in differences in groundnuts and maize for aflatoxin prevention.

Investigations on other foodborne diseases due to adventitious toxic material in food

<u>Epidemic dropsy:</u> Several epidemic dropsy outbreaks had occurred in India mainly due to accidental contamination of mustard seed with *Argemone mexicana* seeds. However, the occurrence of these outbreaks due to intentional adulteration of mustard oils has been reported during early 70s in various regions of Andhra Pradesh¹⁷. On the basis of experiments on monkeys, the minimal toxic dose of argemone oil and permissible limits of argemone oil in edible oils could be established¹⁸. The development of a simple and sensitive test that permitted the quantification of argemone oil in edible oils at 0.1 per cent was a significant achievement¹⁹.

<u>Veno-occlusive disease</u>: The investigations of veno-occlusive disease that had occurred in tribal villages of Madhya Pradesh during 1975 claiming 28 lives revealed the nature and potential for contamination of staple millets such as *Panicum miliare* with toxic weeds of *Crotolaria* species containing pyrrolizidine alkaloids²⁰. The level of alkaloid consumption up to 40 mg resulting from a contamination level of two per cent in the millet was estimated to have caused veno-occlusive disease in man²⁰.

Other investigations on natural toxicants & contributions

Toxicological investigations on unconventional plant oils for edible purposes: Various studies were undertaken to evaluate the unconventional sources of plant foods especially for use as edible oil sources that could facilitate in overcoming edible oil shortage in the country. Detailed investigations were carried out on the chemical, nutritional and toxicological properties of unconventional oil sources identified *viz*. seed oils of *Cleome viscosa*, mango kernel, *Terminalia bellerica* kernel, rice bran oil, crude palm oil, *mahua* oil and debitterized neem oil as potential sources of edible oils²¹.

Identifying natural sources of plant gums that could be used as food additives

Toxicological investigations of naturally occurring plant gums, namely gum karaya (*Sterculia urens*) in Rhesus monkeys established its safety for human consumption²² and led to its acceptance as a food additive by the Joint Expert Committee of Food Additives of the WHO/FAO enabling unhindered export of the produce from India²³.

Testing the safety of damaged or discoloured food grains

The Institute made important findings of food safety concerns of food grains that were discoloured or damaged particularly during post-harvest processing and storage which played a major role in preventing food waste and protecting economy especially in large storage of food grains. Examples are the work on Karnal Bunt affected wheat grains²⁴, black tip rice grains of rice variety Phalguna²⁵, and the rain damaged paddy containing permissible levels of aflatoxins²⁶. The findings of fungal and aflatoxin contamination below the maximum permissible levels were important in release of the stored rice for public distribution system by the Government of India²⁶.

Work on food safety for protection of public health: An important transition

With increase in the volume of international trade in food, newer contaminants in the food chain in addition to persisting traditional ones became the global focus. Recognizing the importance and relevance of global developments and their impact on health of the consumer as well as nation's economy, various food safety issues both at domestic level and internationally traded commodities were targeted and important initiatives for evolving a national strategy for food safety and quality control developed.

Development of national strategies for food safety control

The Institute played a major role in evolving national strategy for food safety and quality control as evidenced from two major national workshops on food safety that attained national recognition: (*i*) Workshop on National strategy for food quality control held in 1981 that brought out several challenges in the present food system highlighting the problems in the food supply chain, infrastructure deficiencies and requirements, appropriate orientation of research and development efforts to improve the food system, importance of education and raising consumer awareness of food safety and extent of networking and cooperation between government, industry and trade for ensuring food safety to the consumer²⁷. The major recommendation was for the establishment of a single food agency by bringing all food quality control activities and agencies under a single statute and implementing agency. (ii) National workshop on food safety in public catering organized in 1992 reviewed the existing situation and suggested uniform guidelines for licensing, grading, inspection of public catering establishments on hygiene basis, identification of information and education and communication to ensure food safety in mass catering²⁸. The work carried out by the Institute on street foods resulted in a global compendium on street foods published by the Karger Press, Basel, Switzerland²⁹.

Expanding the scope of studies on food toxins & food contaminants

The scope of studies on food toxins was broadened with the identification of a wide range of food safety risks derived from various food contaminants that impacted both health and economy of the nation and were brought under the investigation regime. These were foodborne bacterial pathogens, waterborne zoonotic parasites, fungi and mycotoxins, aquatic biotoxins, pesticide residues, heavy metals, veterinary drug residues, adulterants, use of food additives in processed foods and use of new technologies for food production³⁰. The main thrust of the Institute was to fill the gap of paucity of reliable data with regard to the extent and nature of food contamination. An important development in this regard was evolving risk-based approaches for addressing food risks chiefly risk assessment, risk management and risk communication approaches. In this context, food contamination monitoring studies were initiated using a uniform sampling methodology unlike the purposive biased sampling procedures used in earlier investigations on foodborne disease outbreaks. The main aim was to assess extent of contamination under normal circumstances by aflatoxins, pesticide residues and heavy metals in selected foods, identify high-risk commodities and strengthen laboratory analytical quality assurance in the analysis of food contaminants³¹. The NIN in recognition of its work on aflatoxins

was appointed as the coordinator of aflatoxin studies under these programmes. Through these programmes, significant work was accomplished at the national level in identifying maize, groundnut and parboiled rice as high-risk commodities to aflatoxin contamination. The programme also identified milk and infant foods as high-risk sources for pesticide and heavy metal contamination.

Investigations on specific foodborne disease outbreaks with circumstantial evidence

The Institute raised awareness of the problem of food contamination and associated risks of foodborne diseases among food control authorities as well as consumers by identifying several foodborne disease outbreaks wherein the specific cause was not immediately known. Through systematic epidemiological investigations together with collection and analysis of food and biological samples for possible chemical contaminants, the cause of foodborne diseases could be successfully established. Important among these investigations were outbreaks due to algal toxins through the consumption of contaminated fish, accidental poisoning of rice with chemicals such as sodium nitrite, leaching of copper and tin into rice cooked in improperly coated cooking vessels and consumption of rancid biscuits by children³⁰. Apart from these threats, emerging health threats were identified from region-specific local indigenous foods and habits. Important among these were chewing of mixtures of nut powder and tobacco in the form of pan masala/gutka that were associated with symptoms of oral submucous fibrosis especially in young adult individuals³². The study on the economic cost of a foodborne disease caused by a bacterial pathogen indicated that the cost in India was much more than the USA and had attracted global attention as it was the only study of its kind from a developing country³³.

Investigations on newer adulterants

The Institute was instrumental in identifying newer adulterants apart from the traditional/conventional ones and performing toxicological studies and developing methods for their detection. Some important adulterants identified were fraudulent use of colours in food matrices that are not permitted for such addition, use of aluminium foil in place of silver foil on sweets, *pan* masala, coal tar dyes especially in confectionery, edible oil with castor oil, indiscriminate use of veterinary drug residues, ultramarine blue in dry ginger, non-permitted malachite green in *saunf* (*Pimpinella anisum*), unconventional toxic legumes in commonly consumed pulses, *etc*³⁴.

Assessment of dietary contaminant exposure for risk assessment

It was noted that the level of risk associated with each contaminant would vary depending on the frequency and quantity of food consumed and the methodology used for assessing dietary contaminant intake35. These findings had much relevance to establishing maximum limits for contaminants in foods such as aflatoxins whose dietary exposure varies depending on consumption as staple or non-staple foods, such as spices. Studies on exposure to food colours in confectionery emphasized the need to fix maximum limits based on the extent of consumption of such foods³⁶. Festival seasons were identified to be high-risk periods where intake of foods with colours could be high. Exposure assessments using total diet study approach for assessing total contaminant exposure in the Indian context was identified as a practical approach since it focused on contaminants in the total diet and not on individual foods³⁷.

Studies on microbial pathogens

The Institute identified the application of Hazard Analysis Critical Control Point system in controlling microbial pathogens in the manufacture of indigenous foods particularly in the unorganized sector as well as in the shrimp industry³⁸. By identifying critical control points in the production and manufacture of these foods, factors influencing microbial contamination at each step in the production process could be satisfactorily controlled. Identification of several pathogenic organisms in street food sector helped raise awareness of the importance of hygienic practices in handling and preparation of food. The institute gained recognition for its work on foodborne pathogens and was appointed as the nodal centre for a study on Knowledge, Attitude, Beliefs and Practices on Food Safety and Drugs in Rural and Urban slum populations in all States of India by the Ministry of Health and Family Welfare during 2005-2006³⁹. An important finding from the study was the high prevalence of foodborne diseases at the household and community level in spite of good knowledge on food safety and personal hygiene practices³⁹. On the basis of these findings, the Institute initiated several Knowledge Attitude and Practices (KAP) based surveys of consumers on foodborne pathogens and food safety to document factors influencing food safety at the household and community level as well as to raise awareness of food safety and preventive measures to reduce food contamination and disease.

Studies on pesticide residues in food and water

An important investigation was on the analysis of pesticide residues in sugar samples used for the manufacture of carbonated beverages through a multicentric study in the year 2004 at the request of the Joint Parliamentary Committee constituted by the Parliament. The results indicated that sugar samples were free of any pesticide residues⁴⁰. Methods of analysis of pesticide residues in different food matrices using advanced analytical methods based on mass spectrum have been developed and used successfully for testing vegetables, fruits and other foods⁴¹.

Establishment of infrastructure for safety assessment & testing of genetically engineered (GE) foods

Several important food safety issues associated with genetically engineered (GE) crops that were relevant to the Indian context were identified which played a major role in developing protocols for premarket safety assessment of GE crops. Based on these protocols safety assessment guidelines were brought out by the ICMR for GE crops that would be marketed in India⁴². The Institute became the first public sector laboratory to have necessary infrastructure for food safety assessment of new technologies for food production chiefly GE foods on the basis of international standards. Through this facility, the toxicity and allergenicity risks of various genetically modified crops are evaluated as part of their pre-market food safety approval by the regulatory authorities.

Conclusions & way ahead for management of food safety risks in India

A variety of food toxicants, contaminants and adulterants that have been found to be responsible for several foodborne disease outbreaks and problems of ill health in humans and animals have gained wide international recognition. The work accomplished by the NIN over a 100 years period need to be viewed from the perspective of various challenges in the food system in India that have profound impact on food safety. Currently, these challenges are attaining a new dimension with the introduction of global food safety assurance approaches through risk management of food safety risks in the whole food chain from production to consumption. A risk management framework taking a whole food chain approach for addressing various food safety hazards/issues with documented policies and procedures needs to be evolved to identify and prioritize food safety issues. There is an urgent need in India to understand food safety risks to consumers and risk-based approaches are needed for various activities related to food safety issues of national importance⁴³.

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