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ICMR BULLETIN

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HEALTH HAZARDS OF FUMONISIN MYCOTOXINS AND ITS PREVENTION

Safe, adequate and nutritious food intake is an essential pre-requisite for maintaining good health. A variety of naturally occurring food contaminants like mycotoxins constantly pose a threat to human health. Mycotoxins, the secondary metabolites produced by fungi have gained considerable health and economic significance during the last four decades. Application of the risk analysis approach to food safety issues revealed the need for assessing the occurrence of mycotoxins in various food items, particularly in staple cereals. The National Institute of Nutrition (NIN), Hyderabad, has been investigating outbreaks of food-borne disease due to the consumption of mycotoxin-contaminated food commodities. These include aflatoxic hepatitis in parts of Gujarat and Rajasthan, enteroergotism in Rajasthan and acute deoxynivalenol mycotoxicosis in the Kashmir Valley due to the consumption of mouldy maize, ergoty bajra and rain damaged wheat respectively[1-3].

Fumonisin Mycotoxins

Fumonisins are a group of mycotoxins produced by species of *Fusarium*, mainly *F. moniliforme*[4]. The discovery of fumonisins in 1988 by researchers from the South African Medical Research Council received world-wide attention[5]. Chemically, fumonisins are diesters of propane 1,2,3 tricarboxylic acid and are structurally similar to sphingosine produced by *F. moniliforme* and related species in agricultural commodities, in the field as well as during storage. Although different fumonisins *viz* fumonisin A_1, A_2, B_1, B_2, B_3, B_4 and C_1 have been reported, only fumonisin B_1, B_2 and B_3 were found to occur naturally in foods[6]. Among the different varieties, fumonisin B_1 is the major metabolite occurring naturally, mostly in maize. Fumonisins have been shown to be hepatotoxic, hepatocarcinogenic and nephrotoxic to rats, atherogenic to monkeys and also lead to poor weight gain, diarrhoea and rickets in broiler poultry[7]. Fumonisins are shown to cause developmental toxicity in rats, mice and hamsters, and are toxic to chick embryos[8]. Studies have shown that fumonisins are cytotoxic to different mammalian cell lines *in vitro*, although the sensitivity differs between different cell lines[9]. Fumonisin B_1 has been found to inhibit the *de novo* sphingolipid synthesis both *in vitro* and *in vivo*[10,11]. The International Agency for Research on Cancer (IARC) has classified fumonisin B_1 under the 2B group of carcinogens, *ie*, "possibly carcinogenic". In view of its potential toxic effects[12], a study has been initiated to find out the relevance of fumonisins in the Indian context.

Natural Occurrence

Fumonisins have been shown to occur naturally in maize and maize-based animal feeds throughout the world

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in levels ranging from a few nanograms to a few hundred micrograms[7]. In general, maize and its products meant for animal consumption, contain higher levels of fumonisin B_1. Maize has been shown to be a good substrate for many of the mycotoxins. Maize is not only consumed as a staple by certain segments of the Indian population, but also used as an important ingredient in animal feed.

A total of 157 samples consisting of maize, sorghum, poultry feeds and horse feeds collected from northern and southern parts of India, were analysed using high performance liquid chromatography (HPLC) for the possible presence of mycotoxins like fumonisin B_1 and aflatoxin B_1. Detection limits were 20 ng/g for fumonisin B_1 and 1.5 ng/g for aflatoxin B_1. Their levels in maize, sorghum and poultry feeds are given in the Table. Maize showed higher fumonisin B_1 contamination than sorghum[13]. All the rain affected maize and sorghum samples showed fumonisin B_1 contamination, whereas 74% of the normal maize and 4.5% of the normal sorghum samples contained fumonisin B_1. Highest fumonisin B_1 level was seen in a rain-affected maize sample (64.7µg/g). Though aflatoxins were found to co-occur, no correlation was observed between fumonisin B_1 and aflatoxin B_1 indicating that both the toxins exist independently in the samples.

In comparison with sorghum, maize samples showed higher contamination with *Fusarium* sp. In addition, highest number (16/26) of *Fusarium* species belonging to the section *Liseola* were isolated from the maize samples. Majority of the isolates (19/26) belonged to *F. moniliforme*. Most of the isolates from maize (15/16) produced fumonisin B_1. Highest fumonisin B_1 production was seen with *F. moniliforme* isolate from feed (234µg/g). In general, *Fusarium* isolates from maize produced higher fumonisin B_1 than the isolates from sorghum.

Table : Incidence and levels of fumonisin B_1 and aflatoxin B_1 in different commodities.

Commodity	Fumonisin B_1			Aflatoxin B_1		
	Incidence (positives/ total)	Range (µg/g)	Geometric mean (µg/g)	Incidence (positives/ total)	Range (µg/kg)	Geometric mean (µg/kg)
Normal sorghum	2 / 44	0.15 - 0.51	0.27	9 / 44	0.18 - 30.34	1.97
Rain affected sorghum	25 / 25	0.07 - 7.80	0.48	24 / 25	2.0 - 830.00	24.01
Normal maize	26 / 35	0.01 - 4.74	0.62	31 / 35	0.11 - 4030.47	2.60
Rain affected maize	19 / 19	0.04 - 64.7	1.17	19 / 19	5.0 - 126.00	14.38
Poultry feeds	5 / 14	0.02 - 0.26	0.10	14 / 14	0.38 - 108.61	37.88

Substrate Specificity

Studies carried out on the production of fumonisin B_1 in maize[14] in the laboratory by different workers[15] revealed that maximum fumonisin B_1 production occurs when inoculated maize is incubated at 25°C for 7 to 9 weeks. However, considerable growth and fumonisin B_1 production was seen in the first week of inoculation itself. As high as 15 µg/g of fumonisin B_1 production by *F. moniliforme* strain MRC 826 in maize has been reported under similar conditions. In order to study the fumonisin production in different cereal substrates such as maize, rice, sorghum and wheat in the laboratory, sterilized substrates were inoculated with fumonisin producing strain of *F. moniliforme* and incubated in the dark for various intervals upto 60 days at 25°C. Results revealed that all the substrates supported good fungal growth, although they varied greatly in their capacity to support fumonisin B_1 production. The Figure shows the production of fumonisin B_1 on different substrates at the end of 60 days of incubation. Highest fumonisin B_1 production (2101 µg/g) was seen in maize followed by rice (1448 µg/g), sorghum (125 µg/g) and least in wheat (31 µg/g). Rapid production of fumonisin B_1 was seen from 10 days onwards in maize, 20 days onwards in rice and was tardy throughout in wheat and sorghum. Although production of fumonisin B_1 in rice was seen to be tardy during the first 10 days of incubation, its production increased rapidly by the end of 60 days of incubation. The reported variation in the production of fumonisin may be due to the differential availability of

various intermediates required in the biosynthetic pathway or the presence of inhibiting compounds in wheat and sorghum[14].

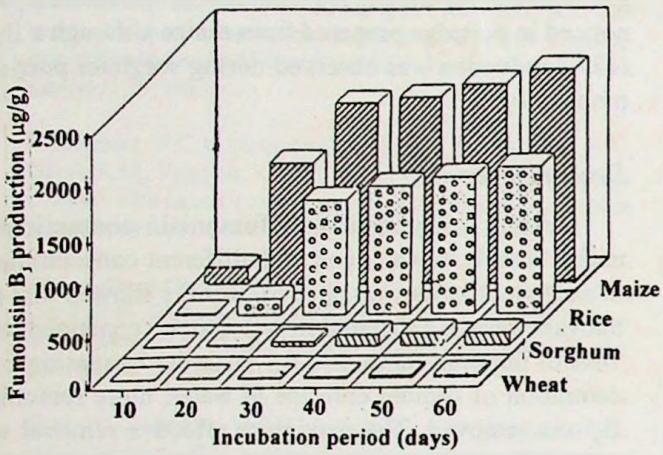


Fig. Fumonisin B_1 production on different substrates.

Health Implications

Though consumption of maize contaminated with fungus *F. moniliforme* has been traditionally associated with human and animal health hazards, the toxin responsible for these effects was not identified till the discovery of fumonisins. The two major diseases associated with fumonisins are leukoencephalomalacia in horses and pulmonary oedema in pigs. Leukoencephalomalacia is characterized by degeneration of white matter of the brain. Horses are the most sensitive animals for the fumonisin toxicity and levels as low as 8 µg/g in the feed may be fatal. Pulmonary oedema and hydrothorax, a fatal syndrome in pigs has been reported from different parts of the world[16]. Of late, field outbreaks of leukoencephalomalacia and pulmonary oedema have also been reported from USA[16]. However, so far such incidences have not been reported from India.

Disease Outbreak in Humans

During October 1995, there were unseasonal rains in certain parts of the Deccan Plateau at the time of harvesting the *Kharif* crops of maize and sorghum. Heaps of harvested maize and sorghum were left in the field for about 10 days. Due to improper storage, these crops got affected by moulds and when food items prepared from these mouldy grains were consumed by animals as well as humans, disease outbreaks were reported. There were reports of deaths of domestic animals and of an acute disease outbreak in humans living in the affected region. A rapid epidemiological survey was conducted in 50 villages belonging to 6 districts of Andhra Pradesh and Karnataka states of southern India. The disease was characterized by borborygmy, abdominal pain and diarrhoea. The problem has been traced to the consumption of food prepared from mouldy sorghum and maize. The disease persisted as long as mouldy grains were consumed. However, those who had access to alternative foods, did not show the symptoms of disease. Fortunately the disease was self-limiting, non-contagious and not fatal. Though people were aware of the cause of the disease, they continued to consume mould affected grains as its consumption was not considered by them to be life endangering. Besides, they did not have any alternative food source. The disease occurred in the poorest segments of the population such as marginal farmers and agricultural labourers. High levels of fumonisin B_1 was found in the maize (upto 65 µg/g) and sorghum (8 µg/g) collected from the affected households, whereas these levels were comparatively lower in the unaffected households. Samples did not contain any other *fusarium* mycotoxins and had low levels of aflatoxin B_1[17].

Disease Outbreak in Poultry

During the study period, it was observed that rain affected mouldy maize was purchased by middlemen to be used as poultry feed ingredient after mixing with normal grains. Hence, a few farms in the region were visited to find out the possibility of disease outbreak which occurred only in two layer poultry farms. The disease was characterized by black sticky diarrhoea, reduced weight gain, drastic drop in egg production, lameness and mortality. Antibiotic and vitamin supplementation had no effect. Feed withdrawal showed improvement. The cause for the disease outbreak was traced to a fresh batch of feed containing high levels of fumonisin B_1 (8.5 µg/g). Some of the symptoms were reproduced by giving the incriminated feed to cockerels and fumonisin B_1 containing culture material to layer hens in the laboratory[18].

Oesophageal Cancer and Fumonisins

Fumonisins have been epidemiologically correlated with the high incidence of human oesophageal cancer in certain parts of the world such as South Africa[19] and China[20]. The highest incidence of human oesophageal cancer has been reported from the lower Assam region of India. This region comes under the Dibrugarh Hospital Cancer Registry[21]. To find out whether fumonisin has any role in the etiology of oesophageal cancer in the region, a survey was conducted with the cooperation of the Regional Medical Research Centre, Dibrugarh. However, none of the food samples tested contained detectable fumonisin

B_1 indicating that fumonisin may not have any role in the etiology. Other possible etiological factors investigated include a special food ingredient called *Kalakhar*, a highly alkaline coffee-decoction like liquid made from the charred banana false stem. This product is frequently used in the lower Assam region. Being highly alkaline and a charred product, it may play a role in the etiology of the oesophageal cancer. This problem required further study. During the study, the role of food and domestic environment in the etiology was studied by investigating the incidence of oesophageal tumours in the domestic poultry population in the region. Interestingly, 9 of 680 oesophagi collected from the region showed visible tumours. Histopathological study of the samples revealed that they were pseudo tumours. While samples collected from the Hyderabad region did not show any visible tumours, the oesophagi from the lower Assam region showed histopathological changes such as basal cell hyperplasia, glandular hypertrophy, acanthosis and reactive changes. Hence, these results suggest that food and domestic environment might play a major role in the etiology of human oesophageal cancer in the region (unpublished observation).

Detection Methods

There are a number of methods available for the detection and quantitation of fumonisins in food samples. Methods include TLC, HPLC, GC and ELISA[22,23]. The HPLC procedure with the ophthaladehyde derivatization is widely used. During the epidemiological survey of human disease outbreak, the need of a method for the detection and quantitation of fumonisin B_1 in human urine was recognised as there is no sensitive method available. A two-step HPLC clean up method was developed with an additional non-ionic polymeric absorbant resin Amberlite XAD-2 clean up before the strong anion exchange (SAX) cartridge clean up. The presently available method involved a single step SAX cartridge clean up and was not found to be suitable for human urine with large volume at low toxin levels due to salt interference. The newly developed method had detection limit of less than 8 ng/ml with a high recovery and reproducibility[24].

Prevention and Control Strategies

Effect of cooking

Effect of household cooking processes such as preparation of unleavened Indian bread *(roti)* and porridge made out of naturally contaminated maize and sorghum on fumonisin levels was studied by simulating household cooking conditions in the laboratory. During preparation of unleavened Indian bread upto 29% reduction in toxin was seen in maize and no reduction was observed in sorghum based preparation. No reduction in fumonisin B_1 was noticed in porridge prepared from maize although a little (12%) reduction was observed during sorghum porridge preparation[25].

Decontamination

Density seggregation of fumonisin-contaminated maize kernels in water and with different concentrations of sodium chloride was studied. Results showed that the buoyant kernels separated in water alone contained upto 74% of the total fumonisin B_1. With the increasing concentration of sodium chloride in water, more fumonisin B_1 was removed. The maximum effective removal was upto 86% with saturated NaCL solution. Removal of fumonisin B_1 in 30% NaCL was optimal, as it was not significantly different from the saturated NaCL solution[26].

Varietal differences

To assess the susceptibility to fumonisin B_1, 10 genotypes of maize consisting of 5 inbred and 5 hybrid varieties were screened. A large variation was seen among different varieties with respect to fungal growth and fumonisin B_1 production in the laboratory. Two inbreds *viz Trishula* and *Harsha* and one hybrid, 5015x5016 supported very low production of fumonisin B_1 (<200 µg/g) and all the remaining genotypes supported production of high level of fumonisin B_1 (>1200 µg/g)[27].

Conclusions

Maize is the high risk commodity for fumonisin B_1 contamination. Although low levels of fumonisin B_1 were found in sorghum, high levels may accumulate under conditions favourable for mould growth. Fumonisin producing capacity of the Indian isolates indicates the need for control of fungal contamination in the field and at the post-harvest level. Naturally occurring fumonisin B_1 levels in maize and sorghum also can cause health disorders in humans and poultry. Cooking does not result in considerable loss of fumonisin B_1. However, fumonisin levels can be effectively controlled by the available procedures of decontamination.

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This write-up has been adapted from the article entitled "Health hazards of fumonisin mycotoxins and its prevention" by Sh. P.H. Shetty, Senior Research Fellow and Dr. Ramesh V. Bhat, Dy. Director (Sr.Grade), published in the *Nutrition News* 18(3), 1997.

ABSTRACTS

Some Research Projects Completed Recently

Effect of low level prenatal and neonatal irradiation on the adult brain development and reproductive function in mouse.

The study was carried out on inbred Swiss albino mice to evaluate the effect of gamma irradiation at selected critical developmental stages during gestation on the adult neurophysiology and to see, if the neurophysiological effects of prenatal irradiation persist to later part of life. Efforts were also made to find out if prenatal irradiation would impair the reproductive performance of mouse.

Pregnant mice were whole body irradiated with 0.25, 0.35 or 0.5 Gy of gamma radiation on days 11.5, 12.5 (late organogenesis days), 14.5 or 17.5 (foetal days) post coitus (pc) and allowed to complete gestation and parturate. Behavioural and haematological changes were studied in the adults at 6,12 and 18 months of age. Reproductive performance was tested at 6-8 months of age after mating the irradiated F_1 males with normal females of the same age. For neonatal exposure, pups were whole body exposed to 0.5 Gy of gamma radiation on days 4,5 or 6 post-partum.

Adult behaviour was not affected by prenatal irradiation with 0.25 Gy. Exposure to 0.5 Gy on days 11.5, 12.5 or 14.5 pc produced significant changes in the exploratory, locomotor and learning and memory performances at 6 months of age. The changes were more pronounced after irradiation on the late organogenesis days (11.5 and 12.5 pc) than on the foetal day (14.5 pc). Normal brain function was restored by 12 months in all animals, except those exposed on 11.5 day pc in which the impaired locomotor activity and learning deficiency persisted even at 12 months of age. Even 0.35 Gy on day 11.5 pc produced a significant change in the locomotor and learning performance of the young adult mice. Animals born to mice irradiated on day 17.5 pc were more resistant to these effects. The peripheral RBC counts and haemoglobin showed significant decrease at 6 months of age when the pregnant mouse was exposed to 0.5 Gy on the foetal gestation (14.5 or 17.5 pc) days, but not during the organogenesis period. Post-partum exposure did not have any significant effect on the adult behaviour or haematological parameters. None of the hippocampal biogenic amines (noradrenaline, dopamine, 5-hydroxytryptomine and its metabolite – 5-hydroxyindolacetic acid) studied showed any significant change after any level of exposure on any of the gestation days.

The reproductive performance of the F_1 males exposed to different doses of irradiation did not show any significant change from normal.

It is clear from the study that the late organogenesis period, especially day 11.5 pc is a particularly sensitive phase in brain development and long lasting behavioural changes can be produced in the adult by exposure at this stage to doses below 1Gy.

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Publications:

1. Bhaskar, R., Uma Devi, P., Nalini, N. and Shivananda, B. Age dependent changes in body weight, brain weight, behaviour and biogenic amines in the hippocampus of mouse. *Indian J Gerontol 9(3&4):* 51, 1955.

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Lung specific liposomes as drug delivery vehicles.

The study was carried out to formulate liposomes with increased affinity for lung tissues and decreased uptake by liver and spleen and to evaluate the chemotherapeutic efficacy of antitubercular drugs encapsulated in these liposomes, against experimental tuberculosis in mice.

Surface modification of stealth liposomes by tagging O-stearyl amylopectin (O-SAP) resulted in increased affinity towards lung tissue of mice. Liposomes containing egg phosphatidyl-choline (ePC) and cholesterol (CH) in a molar ratio of 2:1.5 were found to be stable in serum. Inclusion of dicetylphosphate (DCP), O-SAP and monosialoganglioside (GM_1)/distearyl phosphatidylethanolamine-poly (ethylene glycol) 2000 (DSPE-PEG 2000) in PC: CH liposomes further increased the stability in serum.

Tissue distribution of different formulations of liposomes revealed that lung specific stealth liposomes (PC:CH:O-SAP:DCP:GM_1/DSPE-PEG 2000) accumulated more in the lungs than the reticuloendothelial system of mice. The preadministration of PC and CH (2:1.5) liposomes or injections of dextran sulphate (DS) before the administration of lung specific stealth liposomes further enhanced their uptake in the lungs. The behaviour of these liposomes in mice infected with *Mycobacterium tuberculosis* H_{37}Rv was similar to that in normal mice. *In vivo* stability of these liposomes demonstrated slow and controlled release of their encapsulated contents.

Isoniazid and rifampicin encapsulated in liposomes were less toxic to peritoneal and alveolar macrophages compared

to free drugs in spite of their uptake being equal in both the macrophages. Further, the encapsulated drugs, were less hepatotoxic as compared to free drugs.

The chemotherapeutic efficacy of isoniazid and rifampicin entrapped in lung specific stealth liposomes was evaluated by injecting the liposomal and free drugs intravenously twice a week, for six weeks to tuberculous mice. Liposome encapsulated drugs at and below therapeutic concentrations were more effective than free drugs on the basis of colony forming units (CFUs). The organomegaly and histopathological studies also demonstrated that liposomal drugs cleared the mycobacteria more efficiently compared to free drugs. Liposomal drugs had marginal hepatotoxicity as seen by the levels of total bilirubin and serum glutamate pyruvate transaminase and alkaline phosphatase.

The study thus demonstrated that lung specific stealth liposome encapsulated antitubercular drugs are more effective against tuberculous infection in mice and seems to be a promising therapeutic approach for the chemotherapy of tuberculosis.

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Publications:

1. Parampal Deol, I., Khuller, G.K., and Joshi, K. Therapeutic efficacies of isoniazid and refampicin encapsulated in lung-specific stealth liposomes against *Mycobacterium tuberculosis* infection induced in mice. *Antimicrob Agents Chemother 41:* 1211, 1997.

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ICMR NEWS

Meetings

Meeting of the Project Advisory Committee on ICRC Leprosy Vaccine Trial was held at New Delhi (May 25, 1998).

Participation of ICMR Scientists in Scientific Events:

Dr. G.P. Chhotray, Asstt. Director, Regional Medical Research Centre, Bhubaneswar, participated in the VIII International Congress on Infectious Diseases at Boston (May 15-18, 1998).

Dr. Dipika Mohanty, Director, Institute of Immunohaematology, Mumbai, participated in the XXIII International Congress of the World Federation of Haemophilia at The Hague (May 17-22, 1998).

Dr. Y. Venkataramana, Research Officer, National Institute of Nutrition, (NIN), Hyderabad, participated in the XXVI FIMS World Congress of Sports Medicine at Orlando (May 30-June 3, 1998).

Dr. K. Vijayaraghavan, Dy. Director (Sr. Grade), NIN, Hyderabad, undertook a Short-term WHO Consultancy on Nutritional Emergencies in Papua New Guinea (May 15-June15, 1998).

ICMR AIDED SYMPOSIA/SEMINARS/WORKSHOPS/COURSES/CONFERENCES

Symposium/Seminar/Workshop/ Course/Conference	Date & Place	Contact Address
National Workshop of Medical Editors and Reviewers in Medical Communication: Peer Review, Ethics and Internet	June 16-18, 1998; (at Pondicherry)	Dr. C. Adithan, Organising Secretary of the Workshop, Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry-605006.
National Conference on Molecular Diagnostics	June 27-29, 1998: (at Thiruvananthapuram)	Dr. P.R. Sudhakaran, Organising Secretary of the Conference, Department of Biochemistry, University of Kerala, Thiruvananthapuram-695581.
International Symposium on Frontiers of Genetics and Development	July 7-8, 1998; (at Bangalore)	Dr. U. Vijayaraghavan, Convenor of the Symposium, Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore-560012.
International Symposium on Temporomandibular Joint Disorders and Chronic Orofacial Pain	October 30-31, 1998; (at Mangalore)	Prof. P.K. Dayal, Organising Secretary of the Symposium, KMC College of Dental Surgery, Mangalore-575001.

COUNCIL'S TRAINING PROGRAMMES FOR 1998-99

Leprosy

At the Central JALMA Institute for Leprosy, Agra:

- Multidrug Therapy Orientation Course in Leprosy for Medical Officers (August 17-28, October 26-November 6; and December 7-18, 1998).

Virology

At the National Institute of Virology, Pune:

- Diploma in Medical Virology (July 1998-May 1999).

Reproductive Biology

At the Institute for Research in Reproduction, Mumbai:

- Workshop on Andrology for Clinicians (November 16-30, 1998)

Endocrinology

At the National Institute of Nutrition, Hyderabad:

- Annual Certificate Course on Endocrinological Techniques and their Applications (August 1-September 15, 1998).

Nutrition

At the National Institute of Nutrition, Hyderabad:

- M.Sc. in Applied Nutrition (June 1, 1998-February 28, 1999).
- Postgraduate Certificate Course in Nutrition (December 1, 1998-February 28, 1999).

Laboratory Animal Technology

At the National Centre for Laboratory Animal Science, National Institute of Nutrition, Hyderabad:

- Training Course for Laboratory Animal Technicians (June 16-July 31, 1998).

Occupational Health

At the National Institute of Occupational Health, Ahmedabad:

- Training Course on Environmental Hygiene Practice (November 16-20, 1998).

Medical Entomology

At the Vector Control Research Centre, Pondicherry:

- Postgraduate Diploma Course in Medical Entomology (from August 10, 1998).

Biomedical Statistics

At the Institute for Research in Medical Statistics, Chennai:

- Basic Course in Statistics for Postgraduate Medical Students (July 1998).
- Basic Course in Statistics for Medical Officers (November 1998).

Haematology

At the Institute of Immunohaematology, Mumbai:

- Training Course in Transfusion Medicine for Blood Bank Medical Officers (August 11-October 9, 1998).
- Training Course in Blood Group Serology and Blood Bank Methodology for Blood Bank Technicians (August 11-September 10, 1998).
- Training Course in Advanced Haematology and Immunohaematology (September 21-October 9, 1998).

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