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Etiologic Studies

Environmental Cancer in the Indian Context

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Summary. There is increasing global concern on the upward trend of cancer attributable to environmental causes. This has found articulate expression in the intensive action programme initiated in developed countries to carry out systematic epidemiological surveillance studies on environmental based cancer, to conduct both short-term and long-term studies on experimental animals on the mechanism of induction and to search for preventive measures.

Of all environmental agents, chemicals which have been introduced by man have received the maximum attention on account of the fact that besides functioning per se as carcinogens, many chemicals can play roles of synergists, promotors, or procarcinogens. The total number of chemicals in wide use today will be more than a million but hardly a thousand of them has been subjected to the vigorous three animal safety evaluation according to Brigg.

Developmental programmes initiated in post-independence India in the last three decades include industrialisation and modernisation of agriculture. So far as industrialisation is concerned, the major units have grown round certain urban centres or in settlements which have become identifiable pockets of high levels of air and water pollution. Data on air pollution inventory provided by NEERI and other agencies indicate a high content of polycyclic hydrocarbons, including 3,4-benzpyrenes especially in Bombay and Calcutta. The marginal health surveys conducted in these metropolitan cities have attempted only correlation between high incidence of respiratory disorders to particulate or gaseous pollutants.

The modernisation of agriculture, particularly boosting of farm productivity, involves greater and greater use of past control chemicals and synthetic fertilisers. Chlorinated pesticides are also being used in massive quantities for controlling vector-borne epidemics. The evidence for an unusually high body burden of organochlorine pesticide residues in Indians has been documented. Many of them have been shown to be carcinogenic to experimental animals. Relatively high levels of residues of organochlorine have been detected in placentae, cord blood, and breast milk.

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The presence of high levels of suspected particulate matter (SPM) made up of industrially released pollutant in industrial areas, or air-borne pollens and microbial or fungal spores or the minute fugitive dust particles is also a problem of concern to us in this country. Besides health effects caused by them per se, they can act as nuclei for absorption of NO_2 released from industrial activity or from bacterial reduction of nitrate fertilisers. Ideal matrices are formed for chain photochemical reaction triggered by solar or other cosmic irradiation giving rise to nitrosamines, free radicals, etc. Water used for potable purposes in some rural areas has been shown to contain relatively high nitrate and nitrite content.

Occupational exposure to carcinogenic chemicals has also received some attention. Sporadic surveys have been conducted for the ulceration of the nose and septum in workers handling chromate salts (valency vi) or bladder tumors in anthracene dyes. Detailed analysis of environment related morbidity and mortality data has not yet been attempted to build models for the purpose of predictive epidemiology. Welders are exposed to fumes of heavy metals including those of chromium and nickel. The intake of nickel through leafy vegetables and hydrogenated vegetable oils has been considered as one possible source of bioaccumulation of this carcinogenic metal.

In the absence of data banks or registry of reliable morbidity/mortality data in humans, the Industrial Toxicology Research Centre has made a partial survey of the dust load of lungs of food animals killed in abbatoirs in the industrial and mining areas of Bihar and West Bengal. Blocking of lymph nodes by dust has been observed in most of the animals and analysis of the dust collected from lung by X-ray fluorescence spectroscopy has revealed the presence of many toxic metals. The Outdoor Occupational Clinic run by the Industrial Toxicology Research Centre in ESI Hospital at Kanpur has recorded cases of skin allergy due to chromium.

Key words: Environmental chemical pollutants – Pesticides – Particulate matter – Occupational exposure

Introduction

As an outsome of the chemical industry in the last four to five decades, the number and variety of chemicals to which man is likely to be exposed today in his working and living environment is exceedingly large. Out of the astronomical figure of 3.5×10^6 chemicals known to man, 25,000–30,000 items are already under production in substantial quantities. The ingenuity of chemists adds another 2,000–3,000 new species every year to this already swollen list. In the decade ending 1978, the global production of synthetic organic chemicals registered a 255% increase. The world output in 1975 of one important group of synthetic products, i.e., plastics, was 40 million tons. About 2,500 individual chemicals are known to be used in various processing operations in the manufacture of plastics (Fishbein 1979). Examples like the above can be multiplied to visualise the proliferation of chemicals and their impact on human life.

The benefits accruing to mankind from the use of chemicals have been generally acknowledged but are often overplayed by their commercial producers. On the other hand, the attendant risks arising out of the potential health hazards associated with the indiscriminate use and diffusion into the environment of some chemicals have not yet been assessed adequately. It is estimated that as much as 90% of all cancer today is related to environmental factors (Anon 1975; WHO Technical Report 1974; Weinhouse 1976; Train 1977; Kraybill 1977; Highland and Schardt 1979; Ames 1979). The list of causative agents includes carcinogenic chemicals which are dispersed in the environment either deliberately or inadvertently. Food additives, drugs, synthetic polymers, agrochemicals, and pesticides belong to the former class. Examples of chemicals of the latter class are pollutants diffused through industrial and agricultural discharges. Human exposure to these agents is most of the time involuntary and unavoidable. However, smoking or the consumption of processed beef constitute voluntary exposures. Along with these, the intake of food and water contaminated with toxic metabolic products of naturally occurring microbes, alkaloids, metals, etc. are also significant factors in the correlation between environment and cancer.

Chemical Pollution in the Indian Context

India truly typifies the complex problems faced by the less developed nations which are on their relentless march towards self-reliance and the attainment of a better standard of living for their people. Developmental programmes initiated in post-independence India include rapid industrialisation and modernisation of agriculture along with integrated social welfare schemes. Although twothirds of our people are still below the poverty line, we have made the incredible achievement of reaching the top eighth position among the highly industrialised nations of the world today. Inspite of this development, environmental pollution, the price one has to pay for rapid industrialisation, has not yet generated in India the same degree of concern as prevalent in the industrial Societies of the West or Japan. Nevertheless, signs of environmental degradation caused by industrial activity are perceptible on the Indian scene, particularly, in certain urban centres where clusters of unplanned industries have grown. The pollution of water resources by discharge of human waste products is considered at present as of more serious consequence to health than contamination by industrial effluents. This trend is also likely to change soon.

Contributions of some pollution-potential industries to the Indian economy are summarised in Tables 1 and 2. Some of the items being manufactured now are entirely new to the Indian environment. The production of traditional items has also shown an upward trend, often five to six times, as compared to the pre-independence period. The output of phthalic anhydride, a starting material for many potentially toxic aromatics, currently, is 23,000 tons and is expected to rise to 43,000 tons by 1983. Vinyl chloride and aromatic intermediates needed by plastics, the synthetic dye, and drug industries are also being produced in large quantities. The installed capacity for the production of synthetic detergents is about 115,000 tons. The growth of synthetic organic chemical industry along with dyestuff industry, chromite mining, and chrome tanning has also been phenomenal.

Table 1. Long-term projections on chemicals and coal (million tons)

	1973–74	1978–79	1985–86
Coal	79	135	238
Crude petroleum	7.7	12.0	15.5
Fertilisers			
Nitrogenous	1.2	4.0	7.0
Phosphatic	0.4	1.3	3.0

Source: Hand Book of Statistics, Tata Services

Table 2. Output of manufacturing industries (registered sector)

	At current prices Rs. crores	
	1970–71	1973–74
Chemicals and products	370.9	558.8
Petroleum products and coal	55.2	59.9

Source: Hand Book of Statistics, Tata Services

Mention must be made also of the reported high content of arsenic as an environmental contaminant particularly in the Panjab region. The source of this pollutant has not yet been identified. We cannot either ignore in this context the ever increasing consumption of synthetic drugs with toxic potential for release from the torture of one ailment or the other. By 1980, our pharmaceutical and drug industry is expected to touch an annual turnover of 1,000 crores of rupees. It may be pointed out that many drugs which have been withdrawn in the West on the basis of their chronic side effects, are still permitted to be prescribed in India. Many can be bought at the counter without even a prescription.

Aspects of Studies Relevant to Environmental Carcinogenesis in Progress in Industrial Toxicology Research Centre, Lucknow

Though not directly related to cancer, some studies in progress in the Industrial Toxicology Research Centre (ITRC) Lucknow, may be of interest to the participants of this Symposium on Environmental Carcinogenesis and those concerned with the discovery and implementation of preventive measures. These studies constitute part of our on-going programme of work and embody an important component of the Charter of our Research Centre, i.e., to function as a national agency committed to the task of identifying problems related to industrial and environmental toxicology.

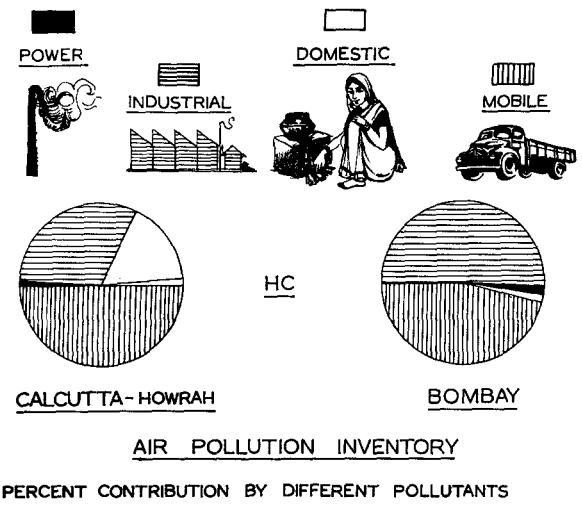

Fig. 1. The profile of polycyclic hydrocarbons in air over Calcutta and Bombay

Epidemiological Surveys

Planned epidemiological surveys to explore health problems arising out of environmental factors are of very recent origin in India. This is surprising in view of the fact that endemic fluorosis both in cattle and humans associated with intake of water with a high content of fluoride has been studied in India quite extensively during the past 50 years. The impact on human health of air pollutants in areas with high air pollution in Bombay or Ahmedabad has been investigated in an exploratory manner, the observations being restricted so far to the profile of bronchitis and lung disorders (Krishna Murti 1978; Sundarsan 1978). The levels of polycyclic hydrocarbons in locations with heavy automobile traffic in metropolitan Bombay, Calcutta, and Ahmedabad are relatively high. Typical figures for hydrocarbons computed from inventories maintained by the National Environmental Engineering Research Institute, Nagpur, as part of the national network of air quality monitoring are shown in Fig. 1. In a study of auto-exhaust pollution carried out by the National Institute of Occupational Health, Ahmedabad, the range of benzpyrene concentrations was found to be from 15 to 32.6 ng/m^3 in summer and from 25 to 3,000 ng/m^3 in winter. From morbidity data the lung cancer cases per 10,000 were also found to be two or three times more in Ahmedabad city than in the surrounding rural area (ICMR 1976). Clinical or experimental studies have not been undertaken in depth so far to correlate the environmental content of these well established carcinogens along with living habits with lung cancer in the two major Indian cities.

We at the Industrial Toxicology Research Centre have been interested to find out how wild birds meet the high level of carcinogenic hydrocarbons in polluted air. Wild pigeons were found to be equipped with hepatic microsomal oxidase systems capable of biotransforming benzpyrene (Fig. 2). The enzyme was subject to induction by phenobarbitone. Birds also showed cytosolic glutathione-S-transferase activities in liver, kidney, and brain which could deal with toxic electrophiles including many known carcinogens (Table 3) (Dikshith et al. in press).

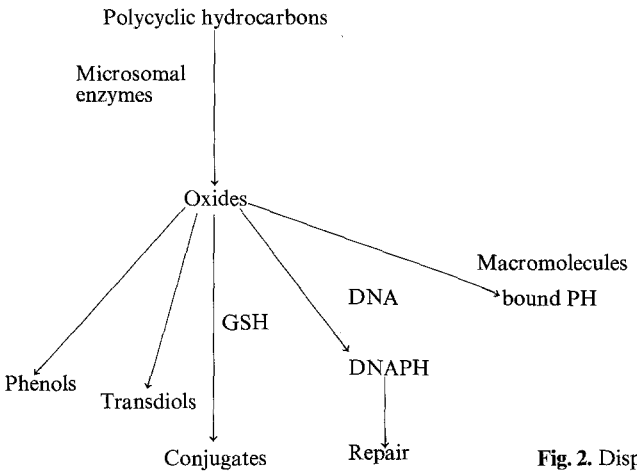

Fig. 2. Disposal of polycyclic hydrocarbons

Survey of Dust Load in Lungs of Food Animals

We have made an attempt to assess the impact of air pollution on the lungs of animals living in the same environment as man. Taking respirable dust accumulating in the tissue as the criterion, we have conducted post-mortem examination of the lungs of food animals like buffalo, sheep, and goat slaughtered in the highly industrialised and mining belts of East Bihar, West Bengal, Utkal, Andhra Pradesh, and Northern Karnataka. As controls we have drawn samples from animals slaughtered in the relatively less industrialised and, therefore, less polluted Terrai region of the Sub-Himalayan tract (Dogra 1979). In Fig. 3 the areas covered in the above survey are shown.

Gross appearance of the tracheobronchial lymph nodes of bovine, caprine, and ovine species from a highly polluted area and relatively non-polluted area is brought out in Figs. 4 and 5. Histopathological examination showed significant changes including inflammation and moderate fibrotic reaction in the lung corresponding to the deposition of particular matter. The blocking of lymph channel

Table 3. Cytosolic glutathione-s-transferase activity (pooled tissue)

Tissue	Specific activity (μmol conjugate formed min^{-1} mg^{-1} $protein^{-1}$)		
	Pigeon	Rat	Pigeon/Rat
Kidney	786	237	3.31
Liver	391	1,625	0.24
Testes	343	1,666	0.20
Brain	178	379	0.46
Lung	123	120	1.02
Heart	101	188	0.53

Substrate: 1 Chloro-2,4-dinitrobenzene

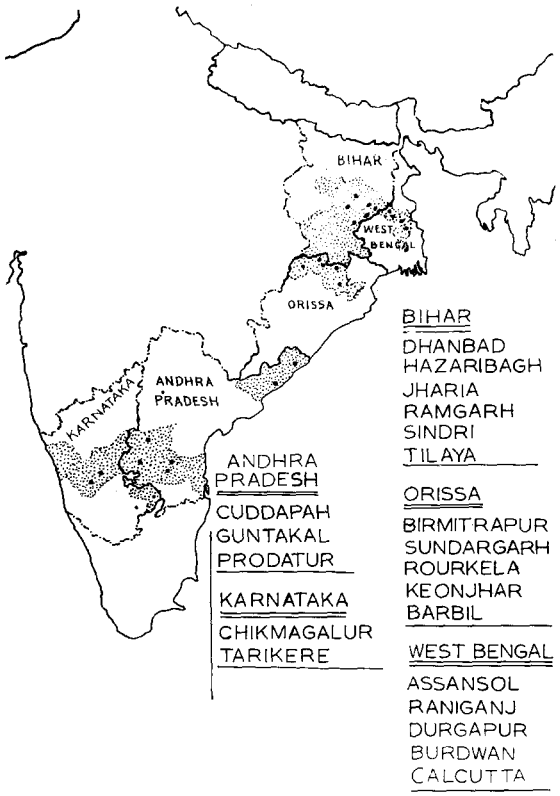

Fig. 3. Map of India showing regions where ITRC conducted dust load surveys in food animals

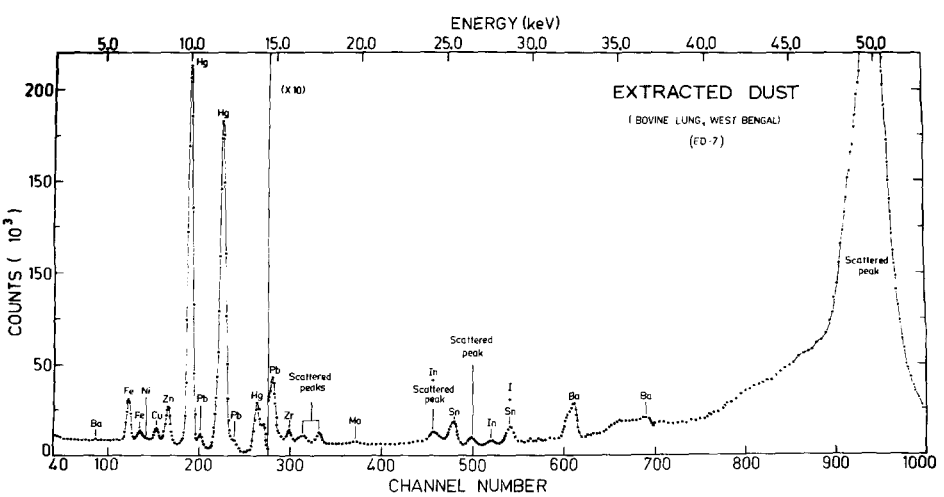

Fig. 4. Trace element profile in lung of buffalos in West Bengal

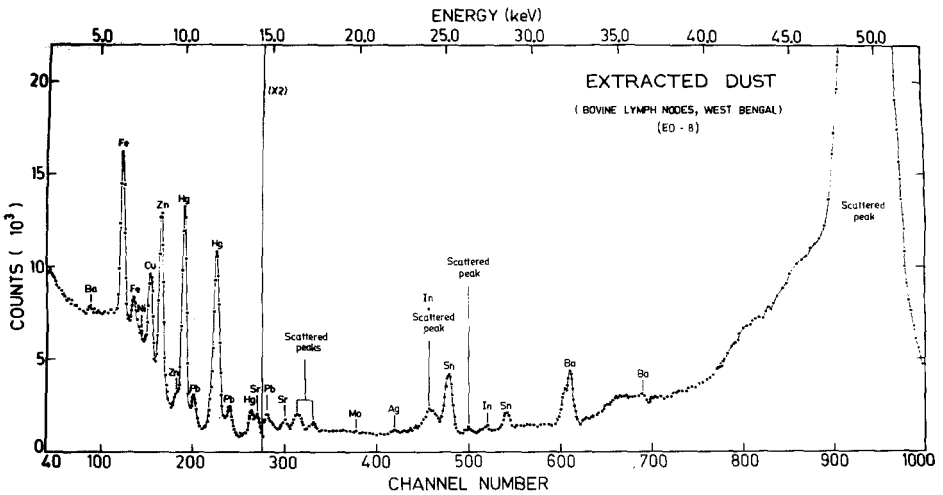

Fig. 5. Trace element profile in lymph node of buffalos in West Bengal

with dust was suggestive of interference with primary immune response. The dust extracted from lungs and the lymph nodes was subjected to X-ray fluorescence spectral analysis. The profile of elements from a highly polluted region in West Bengal is shown in Figs. 4 and 5. The computation of concentration of some of the toxic elements with a carcinogenic potential is given in Table 4 and the tentative conclusions drawn are given in Table 5 (Dwivedi et al. 1978, in press).

Metals had been identified as primary carcinogens as early as 1942 by Schulz and Uehlinger (referred to by Kraybill 1977). The carcinogenic potential and the routes of exposure of nickel have been stressed (Sunderman 1968; Hackett and Sunderman 1969). We in this country have to depend more and more on coal-based energy for our industries and domestic needs. Super-thermal stations based on coal are being set up in West Bengal, Singrauli in South Eastern U.P., Ramgundam in Central India, and at Tuticorin in South India. The preliminary data adduced by

Table 4. Trace elemental concentration (in ppm) of extracted dust

Elements	Lymph node	Lung
Fe	10,300 (1.2)	32,800 (0.5)
Cu	2,300 (1.9)	4,500 (1.3)
Zn	4,500 (1.0)	13,300 (0.5)
Hg	7,000 (0.6)	122,000 (0.1)
Pb	700 (2.4)	4,300 (1.0)
Zr		
Mo	300	
Sn		
Ba		

Values within parentheses represent percentage statistical uncertainities

Table 5. Conclusions of survey of dust load in lungs of domestic animals

1. Studies of lymph nodes from food animals have indicated a strong probability that the human population inhabiting the mining and industrial complexes is likely to be affected by various atmospheric particulate pollutants
2. Study has brought to light the need for greater awareness of the possibility of metal intoxication in human beings since these animals come in their food chain
3. Deposition of excessive amount of inhaled particulate dust containing appreciable quantities of various heavy metals may interfere with the immunological system

us at ITRC points out to the need for the institution of detailed air monitoring in the areas already polluted with toxic metals vapourised by the burning of coal or other fossil fuels. Such studies may provide data to construct predictive models to assess the possible exposure to carcinogenic metals and chemicals of the population inhabiting the region around the proposed sites for the above-mentioned super-thermal stations.

In preliminary surveys conducted at the outdoor Occupational Health Clinic set up by us at Kanpur we have come across cases of skin allergy and other ailments attributable to chromium exposure. The mechanism of carcinogenesis triggered by metal has not been studied as extensively as that caused by organic carcinogens. The mechanism of biotransformation of mercury by transmethylation under anaerobic conditions to yield the most potent methyl mercury has attracted much attention. Studies using purine and pyrimidine bases and native RNA and DNA as metal binding ligands have provided useful guidelines. The intake of toxic metals through drinking water may be very high in the rural population of India and may be of toxicological significance as revealed by the exploratory work conducted by us in the villages of Unnao District of Uttar Pradesh, India following an outbreak of endemic paralysis (ITRC Memoir 1976). The intake of nickel through hydrogenated vegetable oils or of cadmium from food grains harvested from fields treated with high levels of phosphate fertilisers could also be substantial. However, no systematic studies have been conducted to assess the gravity of the problem, if any, and as such we have at best to rely on indirect inferences. It is heartening to report in this context that a detailed nationwide survey programme of environmental pollution by heavy metals is likely to be sponsored soon by the Department of Science and Technology, Government of India.

Residue Analysis of Organochlorine Compounds in Food and Biological Samples

Our Centre has undertaken a random survey of organochlorine residues in feeds, processed foods, and human tissues. As part of follow-up studies on the health of spraymen engaged in the National Malaria Eradication Programme, we have also assisted WHO and national agencies to estimate the body burden of organochlorine pesticides used in vector control. Some of the salient results are summarised in Table 6.

In the absence of precise values for consumption of specific foods by the general population based on consideration of factors such as ethnic differences, age, sex,

Table 6. Presence of DDT in human tissues and some food material

	DDT ppb
Human plasma normal	27.6
Human plasma exposed	199.7
Abdominal adipose fat	1,740.0
Human breast milk	523.0
Farm hen eggs	1,850.0
Chicken liver	535.0
Goat fat	193.0
Mustard oil	960.0
Peanut/vegetable oils	440.0
Coconut oil	124.0

Data based on surveys conducted by ITRC

geographical distribution, traditional habits, etc. the assessment of minimum, maximum, or average intake is rendered extremely difficult. Diet surveys in India due, understandably, to constraints of resources, have dealt hitherto with intake of calories, proteins, fat, vitamins, and essential minerals. The need for extending the survey to enable the computation of intake of toxic substances is, however, being slowly appreciated. In this context it is pertinent to remember that during the peak use of DDT in USA, 85% of the total exposure of the general population to DDT and DDE was via food (Davies and Edmundson 1972).

There is no unequivocal evidence so far to implicate the body burdens of DDT or its metabolites in human cancer. The mobilisation of adipose fat in conditions of stress is likely to bring into circulation a relatively high concentration of DDT residues. The structural resemblance between diethylstilbesterol and op'-DDT has led to the suggestion that op'-DDT can simulate estrogenic effects (Jefferies 1975). Whether such an action of DDT residues can potentiate carcinogenesis is open to speculation. The property of many organochlorine pesticide to interfere with the immune mechanism as known today cannot be ignored either while discussing the long range impact of these chemicals on environmental carcinogens (Table 7).

Experimental tumor produced in mice requires feeding of 140.0 mg/kg body weight per annum for a period of 569 days. If this dose is taken for comparison,

Table 7. Effect of halogenated biphenyls and pesticides on immune response

	Chemical	Species	Parameter	Effect
1.	PCB	G. pig	Antibody response to tetanus toxoid	+
2.	PCB	Rabbit	Antibody response to SRBC	−
3.	PCB	Rabbit	Delayed hypersensitivity	−
4.	Carbaryl	Rabbit	Antibody response to SRBC	−
5.	DDT	Rat	Antibody response to ovalbumin	+
6.	DDT	Rabbit	Antibody response to SRBC	−
7.	DDT	Rabbit	Delayed hypersensitivity	+
8.	DDT	G. pig	Reduction anaphylactic shock	+

Table 8. Colour adulteration in different groups of eatables[a]

Samples		NP-colours	% Adulteration
Milk products	1,154	656	57
Non-milk products	6,182	5,161	83
Pulses	940	940	100
Miscellaneous	4,299	2,063	48
		12,575	70

[a] Khanna et al. (1973) J Fed Sci Technol 10: 33–36 (cited in Khanna and Singh 1975)

Table 9. Approximate consumption of metanil yellow

Coloured items usually consumed	Metanil yellow intake/head/yr (g)
Jalebi	0.79
Shhermal (Tanduri bread – one surface coloured)	0.67
Pulao	0.96
Besan (namkin)	1.05
Bundi Laddu	0.36
Turmeric powder	0.07
Total	3.90
Expressed as intake of p-amino-diphenylamine	1.91

the average daily intake has to be 70.0 mg whereas the actual environmental exposure of man to DDT in USA is less than 0.08 mg daily. About 853 times the average dietary exposure to DDT of human and three times the highest occupational exposure are required to induce cancer in experimental animals. Figures computed from Indian data indicate a total dietary intake per annum of 97.2 mg of DDT by a man of average body weight of 50 kg (Bindra 1972).

Intake of Potentially Carcinogenic Colouring Materials Through Food

Surveys of food adulteration conducted over the last 10 years by our Research Centre have revealed 25–30% of samples examined to be coloured with non-permitted dyes, such as metanil yellow or orange II (Table 8). A rough estimate of the possible annual intake of this compound and through that its toxic metabolite, p-aminodiphenylamine, is given in Table 9. Chronic toxicological evaluation of metanil yellow has indicated that in high doses fed along with diet, the dye causes degeneration of seminal tubules in three species of rodents. The biotransformation of metanil yellow as shown in Fig. 6 leads to the formation of p-aminodiphenylamine as one of the metabolites. Studies conducted at our centre have clearly estab-

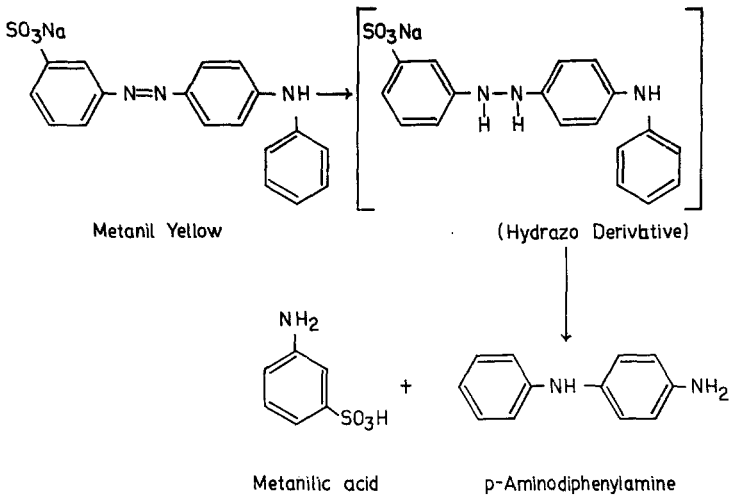

Fig. 6. Azo reduction of metanil yellow and release of p-aminodiphenylamine

lished the ability of this compound to form adducts with proteins by interaction with glutamic acid. In this context it is necessary to stress the fact that p-phenylenediamine, a related chemical used widely in hair dyes, is a well established mutagen and carcinogen (Khanna and Singh 1975).

The total production of synthetic dyestuffs in India in 1977 was around 22,000 tons made by 29 organised sector industries and 2,710 small-scale sector units. The country exported 3,000 tons of dyestuffs in 1974–1975. Carcinogenic dyes like benzidine and β-napthylamine are not permitted to be manufactured. Pollution control of water streams around the factories manufacturing dyes is not, however, strictly enforced. Cancer of the urinary bladder has shown four fold increase after the establishment of the dyestuff industry. In States where the industry is not yet developed, the rate of attack is 0.3% of all cancer of all sites. In Greater Bombay there were 10,382 cases of cancer of all sites out of which 133 were of urinary bladder in 1967–1969. In Panjab among 8,704 cancer cases 97 were cancer of urinary bladder in 1966–1968 (Lobo Mendoca 1977). The possibility of benzidine being released from azodyes in the environment cannot be ruled out at this stage. The European community of Nations has constituted a high level organisation to asses the toxicological and pollution potential of the dyestuff industry. This has led to the banning of the production of benzidine based dyes in Europe but not their import from other countries.

Perspectives

Nitrosoamines formed by dietary nitrites may not be a serious threat in India where the use of nitrites in the curing of meat is not practised. However, the intake of nitrite through water could assume serious proportion. Nitrites produced by reduction of nitrates by soil bacteria can also possibly accumulate in sub-soil water. The concentration of nitrosamines in the environment over cultivated fields can al-

so be significant due to photochemical reaction of nitrites absorbed on suspended particulate matter. We are currently engaged in arriving at realiable estimates of nitrosamines and free radicals in selected rural regions of the country arising out of water and serial photoconversion of nitrites.

The number of chemicals entering the environment today and posing hazardous potential for producing cancer in man has not been computed on a global scale. Approximately 6,000 chemicals have so far been tested in USA for their carcinogenic potential out of which 1,000 have been shown to produce tumors in test animals. The test procedures are very expensive and there is no certainty that the animal data can be extrapolated in all cases to humans. The need for developing simpler, cheaper and reliable predictive in vitro tests to supplement well planned epidemiological surveys has, therefore, to be hardly over emphasised.

As part of the activity of the Central Facility for the Safety Evaluation of Chemicals, an extension of our Research Centre, we have initiated studies aimed at quantitating the mutagenic potential of chemicals by both in vitro and in vivo techniques along with exploring the biotransformation potential of non-mammalian target organisms in order to learn more about the mechanism of action of pro-carcinogens and co-carcinogens. Realising the need for data banks of toxic chemicals, along with other laboratory investigations, we have also made a small beginning to create a nucleus for collection, storage, retrieval, and dissemination of information on the safety of industrial chemicals. Considering the magnitude of the problem our effort so far in this direction is just a drop in the ocean.

Acknowledgement. I am deeply indebted to all my colleagues for providing access to their publications from which I have freely drawn in projecting the above rambling overview of some of our activities with relevance to environmental carcinogenesis.

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