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# Future of Pesticide Industry in India*

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The paper discusses biorational opportunities in synthesis of sterio-chemically oriented insecticides through isochemistry or biosynthesis through genetic engineering. QSAR, natural pest control agents including antibiotics, allelochemicals, semiochemicals the possibility of introducing synergophores and propesticides to circumvent attrition, chemically host mediated defence through macromolecular biotic elicitors in disease control, cloning of resistant crops, regulation of plant growth which will all be thrust areas of research elsewhere.

Fewer pesticides will be available in future. The chance of finding one new pesticide will be 1 in 100,000. It is unlikely that the attractants will gain any large share of market. Development of chemicals which affect development, behaviour and reproduction will be important. There will be conflict with concept of IPM of maximising profit, but not yield. With emphasis on exports, cosmetic effects of pesticides will assume greater importance.

Agricultural pests developing resistance will triple by 2000 AD, leading to pesticide attrition. To circumvent this, mixtures of pesticides may be necessary.

Microbiocides will not be of major importance due to their limitations on survival and spread.

Newer application and formulation techniques will be in vogue, particularly solar powered sprayers and microprocessors controlling droplet size and trajectory. These will need improved formulations and packaging to reduce or eliminate handling of pesticides in the field.

The regulatory requirements will be harmonized and more rational, but being stringent India cannot hope to introduce a new synthetic chemical into world market. The risk assessment will be more pragmatic.

## Population and Food Production

By the end of this century the world population will be more than 6.5 billion. Even to feed people at the present standards that are far from adequate in many parts of the world would involve growing 1½ times as much food as we now produce.

*The views expressed by the author are not necessarily those of the industry or the management

Food supply is not the only problem. The production of raw materials for many industries and non-food crops like rubber, fibres, tobacco, non-essentials like coffee, tea, cocoa and spices which offer the developing regions the opportunity of taking part in the world trade and earning foreign exchange should increase. Agricultural production can be increased by either bringing more land under cultivation or increasing productivity per hectare. Cultivable land is a finite source and FAO estimates show that opening up of more land to farming could make possible only ¼ of the increase in food and fibre production which is needed, 60% of the increase must come from an increase in productivity (Anon. 1983).

Agricultural products (i.e. renewable raw materials) are most likely to become an important source of chemical feed stocks in the forthcoming decades as the availability of fossil resources decline. The increased biomass production will definitely need the support of crop protection chemicals to secure the economics of biomass use for feed stock purposes.

**Pesticide Industry Today in India**

After Japan, India is perhaps the largest manufacturer and consumer of pesticides in the East. The total number of pesticides included in the Schedule to the Insecticides Act is over 380, of which 122 are registered at present and 50 technical grade pesticides are manufactured on an industrial scale in over 30 plants in the country.

Growth of pesticides has been slow in India. We have reached a consumption figure of 60,000 metric tonnes of a.i. (Pesticides for agriculture) in the last thirty years from a modest 2350 metric tonnes in 1955-56. Of this, insecticides account for more than 70% of the total consumption.

It is expected that the world pesticide consumption will increase five fold by 2000 AD with herbicides taking more than 50% of the share (Agnihothrudu 1982). Plant growth regulators are expected to reach a billion dollar market by the turn of the century. In the current year the total pesticide sales at the end user's value is expected to be 4300 million rupees or 0.5% of the world turnover.

It is estimated that on all India basis only 18% of the farmers are taking control measures on pests and diseases. On an average 365 g of pesticides are used per hectare now. Tamil Nadu uses 4.47 kg per hectare. Even assuming that the present day consumption will triple by 2000 AD, the average use of pesticides per hectare will be around 1000 g and the total consumption will be about 160,000 tonnes as against the 60,000 metric tonnes at present.

**Emerging Trends in Pest Control**

Changing agricultural practices and natural or chemically induced shifts in pest population require constant updating of plant protection procedures. The continuing trend in crop monoculture provides a veritable banquet for pest complexes. Increased agricultural production with limited acreage and decreased farm labour supply requires mechanization with maximum assistance from energy and chemical inputs including pesticides. Pesticides often change the balance in the pest populations. These may individually or collectively shift major insect problems, e.g. in cotton from bollworm to stem weevil, in rice from stem borer to plant/leaf hoppers and the attended viruses or in groundnut from tikka to rust or even *Rhizoctonia* root rot.

**Plant Resistance to Insects**

Varieties with multiple resistance will play a major role before the turn of the century.

Plants exposed to long periods of pest attack generally develop defence systems

and produce chemicals that often bind dietary proteins or interfere with digestion. Those with short exposures will have chemicals that involve the biosynthesis of highly toxic agents (Novozhilov 1979). These are areas of coevolution of plants and insects. Plant injury can elicit the biosynthesis of some macromolecular biotic elicitors which are agents of resistance (Keen & Bruegger 1977, Agnihothrudu 1984a, b). There are individual or multiple factor contributions to plant resistance as in tobacco budworm where gossypol and related compounds, several flavonoids, catechins, tannins, cyanidin, delphinidin and their glucosides inhibited growth *in vitro* (Hedin et al. 1980). Here the gene splicing technology will be useful.

**Pesticide Synthesis**

Biorational synthesis of pesticides through computer based design of biologically active molecules will be replacing the conventional random synthesis or isochemistry leading to analogue synthesis. The synthesis will be steriochemically oriented and will be achieved for the most part biosynthetically by incorporating genetic information into microbial or related synthesizers. Attempts will be made to use pesticides at sub microgram levels to control specific life processes like behaviour, reproduction and development. Innovative screening is necessary to assess the activity of insect growth regulators and other semiochemicals (Agnihothrudu 1984c). Future of pyrethroid research would focus on economic consideration and efficacy, control of target and new associations (Martel 1980).

Development of insecticides based on noncholine esterase activity are being pursued based on the chemistry of neurohormones and neurotransmission (Norahashi 1978, 1979). The use of dyes that are subsequently activated by photooxidation in insects is being developed (Carpenter & Heitz 1979).

The identification of enzymes that control specific processes like the neuropeptide proctolin with myogenic activity from cockroach which was inactivated by cockroach enzyme system will be newer approaches. An attempt to the design of enzymes resistant to analogues of proctolin may be useful (Starrat & Steele 1979).

**Pest Control Mechanisms**

Attempts at presticide synthesis which can attack the insect neurotransmission at "novel points" will be more successful in future. The molecular nature of the ionic channels of nerve membrane and interactions have not still been elucidated fully for some insecticides including the pyrethroids. In pheromone perception by insects two different antennal receptors are found involved. These receptors can perceive more than one compound and are sensitive to precise ratios of components. Receptor specificity is further demonstrated in the differential response to chiral forms of pheromones and in responses from receptors of males and females. Messenger-receptor interactions and the role of lipoproteins and sulphydyl groups in the energy transfer may yield valuable clues on pesticide action (Narahasi 1978, 79).

Induced autointoxication and photosensitization through dyes and with acetylenes and furanocoumarins that affect the insect melanins may be one of the areas of fruitful research. Further work on the insect resistance to xenobiotics, the genetic and biochemical basis for cross resistance — nonmicrosomal mechanisms, induction of detoxifying enzyme systems, oxidative metabolism will continue.

**Novel Pest Control Mechanisms**

Recombinant DNA technology has been suggested for introducing genes, for example

genes of chrysanthemum that biosynthesize pyrethroids into other plants. These can be possibly transferred into bacteria which can produce the pesticide that can be harvested.

Cloning for production of resistant crop plants and activation of chemical defence systems against disease in plants are also being actively considered. These include immunization and phytoalexin elicitation. Some plant growth regulators have been shown to increase the content of secondary plant constituents. There is also the possibility of breeding for chemical host plant resistance. Chemical resistance in cotton to several fungi, particularly *Verticillium* Wilt and *Xanthomonas malvacearum* is noticed. The resistant cotton plant biosynthesizes larger amounts of gossypol, hemigossypol and compounds more quickly than the susceptible in response to injury. *Gossypium barbadense* has been shown to possess greater capacity to methylate gossypol terpenoids and to biosynthesize tannins (resistance compounds) than other cotton varieties (Hedin 1982).

**Problems in Development of Novel Compounds**

The rapidly increasing cost of research is one of the main factors in developing novel compounds. Much of this cost is due to the greatly increased regulatory requirements resulting from heightened desire to safeguard man and environment. The development time from discovery to marketing of a pesticide has more than doubled in a decade reaching 10 years.

The new discoveries are complex molecules. They require higher basic cost of manufacture in terms of new plant facilities resulting from more complex synthesis.

The risk involved in developing and marketing a new compound that has much greater initial investment and thus requires a much higher price is further increased by the growing number of highly effective insecticides that are already marketed at a relatively low cost. The speciality products with narrow spectrum of activity which are not favoured by the industry require market acceptance at greatly increased price for a much longer market period to recover initial cost of investment in order to be feasible commercially.

A major problem faced, particularly on an international basis in justifying the risk involved in developing specific compounds desired by the entomologists is the lack of sufficient data for reliable market analysis.

**Integrated Pest Control**

Intensification of agriculture over the last few years, energy crisis and the necessity to take into consideration economic criteria have necessitated revision of pest control strategies and practices. Simply combining different plant protection measures has shifted in favour of the principles of ecosystem control. Further insight into ecological regularities and agrocenosis, leading component relationships, mathematical modelling of the complicated biotic interactions between parasites and phytophagous insects with plants damaged by them should become a theoretical basis for developing control preferences with the use of computers (Agnihothrudu 1984c). In future practical use of existing measures should involve the use of natural factors.

**Natural Pest Control Agents**

Natural pest control agents that modify insect behaviour and those that modify insect growth, development and reproduction will be useful. Food attractants, repellants, feeding stimulants and deterrants, antifeedants, oviposition stimulants and deterrants, toxicants and nutritional factors all of which come under allelochemics will need further investigation. Very little work has been done on the chemokinetic principles like allomones, and kairomones (Rosenthal & Jansen 1979). Toxicants from tropical

and desert plants may be useful as pesticides. Antibiotics like avermectins have been found effective already. J. H mimics, anti J H compounds, reproduction inhibitors, ecdysones, antiecdysones, precocenes, prostaglandins, diapause hormones and chitin inhibitors will be both synthesised and probably isolated from plants (Hedin 1982).

Plant growth regulants in some cases increase the biosynthesis of certain secondary plant constituents. Alpha NAA elicits increased terpene biosynthesis in citrus decreasing attack by fruit flies. Mepiquat chloride a synthetic growth regulator increased tannin content of cotton plants useful in resistance to *Heliothis*.

While phytoalexins are of academic interest, it is doubtful whether they will be of any use in plant protection, unless we have other chemicals that can mediate host defence reactions (Agnihothrudu 1982 & 1983).

**Weed Control**

Herbicides reduce tillage, fertilizer, irrigation, crop losses. It is necessary that we have herbicide synergists. Dalapon reduces cuticular layer of weeds making them more susceptible to thiocarbamates. The mechanism is synergistic. Herbicide safeners like 1, 8-naphthalic anhydride for thiocarbamates are useful and they will play a mojor role in future. Allyl and propargyl amides of oxalic acid and halogenated alkaneic acid amides are also active. Controlled release of herbicides, seed application of herbicides as with EPTC will be useful. Starch xanthate retards release rate from granules of some herbicides. Post emergent graminicides will become very popular.

Modern herbicides interfere with processes such as lipid synthesis with membrane integrity, changes in photosynthetic and mitochondrial electron transport, oxidative phosphorylation, synthesis of pigments, RNA, DNA and proteins and binding of herbicides at the IAA and other growth regulator sites. We should understand better the plant membrane structure and function, the role of membrane turnover and bioenergetic regulation. Chemicals which break the dormancy of weed seeds thus depleting the "Weed bank" will require investigation in depth. Herbicide tolerant plants will be produced through gene splicing or selection. There are reports of gibberellins enhancing effects of bentazon on beans. Herbicide plant growth regulator mixtures may be useful in future.

The nature of the control mechanism and their efficacy for herbicidal activity of secondary plant growth substances such as phenols, aliphatic and aromatic carboxylic acids and their derivatives, steroids, alkaloids, terpenoids, amino acids and lipids is worth investigation further. Allelopathic herbicidal agents sufficiently active are being investigated.

More efficiency in weed control through plant growth regulators that will modulate the whole weed population and not just the seed and vegetative parts of the life cycle—towards which traditional weed control systems is being aimed at. Here chemicals that break dormancy and those that will interfere with vegetative regeneration will be useful.

**Disease Control**

At present the control measures for plant viruses are inadequate and so also for nematodes, soil borne pathogens and bacterial infections.

Modern fungicides have in effect biorationally evolved from the past use of sulphur, copper sulphate, hydrated lime with the result the progress has become evident after the fact it is suggested that we may have to call developments in fungicide research "retrobiorational".

Whether the fungicidal discoveries are "retrobiorational" or "serendipitous" the discovery of biochemical information has lead to discovery of more effective fungicides. Benomyl and thiophanate (benzimidazoles)

act through transformation to alkyl benzimidazole carbamates and the knowledge that derivatives of MBC are potent anthelmintics several phosphorylated thioureas were synthesized and were shown to be active anthelmintics. Chloroacetanilide compounds which were synthesized for herbicidal activity were found to be fungicidal. Ergosterol biosynthetic inhibitors were found to be active on mildews and rusts.

Fungicidal research tends to be relatively general in the range of attack as compared to insecticides and herbicides. Fungicides often kill the beneficial fungi also. The current effort is to elicit chemically host mediated reaction or disruption of host fungal parasite relationship.

A good fungicide should not be phytotoxic, multisite agents are less likely to produce resistance as with sulfenimides. Trialkyltins have great promise. It is surprising that work on modification are sulfenmide molecules is not being done at present. Kohn (1977) has listed eight recorded biochemical mechanisms that are responsible for the antifungal activity of sulfenimides.

Antidifferentiating compounds will be useful and many plant products should be investigated with this end in view. Antisporulants and anticonidiophore compounds will be useful (Agnihothrudu 1983).

**Viruses**

The virus disease development has four distinct phases of infection, multiplication, spread and symptom expression. Attempts will be made to interrupt or inhibit viruses at any of these phases. The most attractive aim for future work is the use of chemicals that restrict normally systemic viruses to local infections. Ribavirin helps eradicate viruses in tissue cultures. The recently discovered chemicals related to aspirin which induced localized acquired resistance in tobacco leaves may also be effective in this system (White & Antoniw 1981).

**Microbial Pesticides**

Burges (1981) has reviewed this aspect of pest control exhaustively. Microbial agents can be used in three ways:

1. They can be introduced to areas where they are absent or rare in the expectation that they will multiply and spread.
2. They can be mass reared and applied to crops.
3. They can be encouraged by manipulation of the environment.

Assuming comparable criteria, the microbials would be worth much less than many chemicals for the industry. Market size and competition are major commercial considerations. The other commercial considerations will be host spectrum, good shelf life, reproducible mechanised technology and modest cost of safety testing and regulatory requirements. Limitations to microbial control are obvious. Fungi do not thrive in dry conditions. B.t. does not spread. A mobile stage limits a pathogen to aquatic environment. UV radiation limits pathogen survival. Each pathogen is to some degree host specific. They have a temperature range. Most fungal propagules are short-lived, unless they are resting spores. Persistence can be a problem with microbial biocides where there is no possibility of cleaning up the environment when once introduced. In our country the protocols for household, veterinary pesticides and microbial biocides have not still been finalised.

**Pesticide Delivery Systems**

Greater awareness of the inefficiency of pesticide application, water supply problems, the need for more rapid and timely treatment and the increased cost of pesticides have stimulated research on new application techniques (Graham Bryce 1983). Pesticide delivery systems are being improved to maximise the activity and reduce adverse effects of pesticides. Elastomeric polymers are being tested

for semiochemicals. Techniques of coacervation or interfacial polymerisation are being used for microencapsulation. Superior carriers and emulsifiers will be used for microemulsions with indefinite shelf life. There are possibilities of using pheromones formulated in conjunction with an insecticide so that insects are attracted to spray deposits.

Changes in packaging like dissolving packs, possible availability of "Pallet spray tank loads", eliminating the need for mixing chemicals on the farm could be achieved in areas with large scale use of pesticides. In view of the increasing fuel and battery costs, significant changes are likely to take place with solar panels for spinning disc sprayers and more efficient photovoltaic cells.

Miniaturization of high voltage generators, control of droplet size and trajectory by electrical forces, the minimal use of energy and the prospect of sprayers with microprocessor controls, all indicate that a major technology is underway (Matthew 1982). With further comminution in droplet size, there will be changes in formulations. There is a greater need for producing high technology formulations like microemulsions, microencapsulations for which new screening and regulatory requirements are possibly needed (Mathews 1979).

**Monitoring**

We must enlarge our knowledge of the toxicokinetic properties of chemicals and their metabolic pathways in aquatic and other organisms which will lead to surveillance programmes reflecting the degree of pesticide burden.

The disposal of pesticides will pose a problem and new procedures should be developed. These may be photochemical conversion, catalytic hydrodechlorination, microwave plasma detoxification, reprocessing, chemical treatment, incineration and bioconversion.

In the analysis of risk factor, multiplication of tests does not imply greater familiarity with risk (Cox & Crammer 1983, Cramer 1983). There is no zero risk on the curve representing the familiarity with a risk in terms of the number of studies carried out is not linear, but inevitably asymptotic. Since risk analysis is one objective building block upon which pesticide regulatory decisions are made, the analytical, metabolic and toxicological studies on which risk assessment is made should be pragmatic. Rapid screening procedures, particularly enzymatic or immunochemical tests need further refinement.

**Pesticide Analysis**

New methodology will reach unprecedented refinement with automated total clean up, final separation and total analysis. Routine, automatic computerised analytical characterization of pesticides and other industrial pollutants will be achieved. Pesticide allergies need more investigation in terms of immunoassays. It is possible now to attach a pesticide to a serum protein of humans, thus forming an antigen. This antigen can be injected into a rabbit to develop antibody titre.

Automatic total method analysis will accept samples and by computer programming provides statistically processed results of multiple analysis. Robots will be used for routine laboratory analysis elsewhere. Personal factor will be reduced. Automated sequencing will enable integrated programmable reactors to perform different functions.

**Pesticide Residues**

The residue problem is exaggerated in public (Agnihothrudu & Mithyantha 1978). Residue expressed at times in ppb (1 g in 1000 metric tonnes) suggest larger quantities than are actually present. Crop protection is only part of agricultural economy. It is agriculture itself that has led to the most fundamental changes in the human environment. Crop protection is thus more a necessary consequence than the cause of environmental

changes. The degree of risk involved in driving a car, crossing a busy street or smoking is far greater than the risk from exposure to pesticides. These are voluntary risks with regulatory decisions taken by the individual. But in the case of pesticide residues in food or water the risk is involuntary and inescapable with unseen bureaucrats making the choice of whether or not to register a pesticide which may carry one in a million risk of cancer.

**Target Specific Pesticides**

The target specific pesticides are not attractive to produce. The developmental efforts and regulatory cost for a specific pesticide are the same as for a broad spectrum chemical. A specific chemical limits opportunities for profits (Samuel et al. 1983).

The build up of resistance is another factor making pesticides less effective. This will lead to pesticide tread mill. Synergophores in synthesis, propesticides and mixtures should receive attention besides synergists (Agnihothrudu 1984b). The problem of chronic toxicity is a possibility with low acute toxicity pesticides which are likely candidates for carcinogenesis.

There is a race between pesticide discovery on one hand and the pesticide attrition due to resistance and restriction on the other hand (Metcalfe & Luckman 1982). The number of agricultural pests developing resistance is doubling very fast and they will triple by 2000 AD.

**Availability of Pesticides in Future**

Fewer pesticides will be available as the requirements for safety and efficacy become greater. Efforts will be concentrated on improving delivery and on IPM for optimum effect with least chemical usage.

The new fourth generation pesticides including pheromones will not gain a large share of market (Agnihothrudu 1982). The increasing emphasis on maximising yields to feed the increasing world population will conflict with IPM which maximises profit, but not necessarily the yields (Agnihothrudu 1984c).

**The Pesticide Controversy**

Public will demand more stringent controls. Increasing levels of sophistication of pesticide chemistry and toxicology will eventually reduce the level of controversy in risk assessment with great confidence. There is a need to reduce adversarial relationships in regulatory divisions with more pervious corporate executive and less recalcitrant bureaucrats.

Chemical pesticides, like any other, innovations by the way are part of modern technology. The dialogue on such serious topics should be deemotionalised. Here the scientists should play a genuine role to whatever party they may belong. One becomes popular accusing agrochemicals. This has been recognised by various politicians of different hues. The mass media should be helpful in starting a purposeful dialogue with scientists. They should come out of the glamour of the negative. What is technically sound, healthy and positive can also serve as headlines, and not necessarily the negative as often happens today.

**Pesticides Regulations and their Impact**

In a number of countries completely illusive terms of patent life are existing. The development of a new product may take ten years. Patent terms of only a few years may not mean any preferential treatment for the originator. This on the contrary is a punishment for his enterpreneurship. Compulsory licencing, unrealistic definitions of the existing regulatory clauses and patents connected with these, automatic lapses or invalidation of registrations, statements and finally, retroactive changes in the interpretations are major factors which could be lethal for any initiative to bring in new chemicals as pirates are beneficiaries under these conditions. On the top of this the easy access to official files

with important basic information obtained by original, tedious, expensive studies by repeat registrants is another threat for introduction of new chemicals. This will lead multinationals to shun new introductions into this country.

**Impact on the Industry**

The more are the tests, the more are the regulatory expenses. A major manufacturer has to spend in the neighbourhood of US $ 500,000 for a chronic feeding study. The real cost of research and development has doubled between 1967 and 1975 and half of this increase is due to regulatory requirements.

Only large transnationals can now afford to undertake innovative research in pesticides as some of them will be tempted to divert investment into areas which are less risky and more rewarding. There is amalgamation of R & D activities worldwide. It follows that more tests on new materials and more reexaminations of existing materials mean less money and fewer scientists available for innovation. Creative discovery is being starved. Regulatory effort is being overfed.

**Impact on the Farmers**

Companies may not register a product for use on a minor crop because of sales for use on that crop will not repay the cost of development and registration. In that event, the farmer has either to accept lower yields and lower quality in the crop because it will not be protected effectively against pest attack. The farmer will have to charge higher prices, or he will have to stop growing the crop. Assuming that each compound controlled only one pest on one crop, the farmer would be faced with the enormous task of timing of applications and storage of pesticides. Under these conditions the farmer will be running a clinic and not a farm, which requires a resident entomologist, plant pathologist, nematologist, to tell him what is wrong with his brinjals, cabbage or til crop and which compound to spray. If the innovative capabilities of the industry decline due to costs, farmers will be left defenceless against the changing form of attack by microbes. Society should be careful not to make demands which could undermine the industry's scientific base or the financial incentives to continue productive work.

**Impact on the Consumer**

The stringent registration requirements give greater protection to the consumer. One should not forget that there is a price not only as part of the cost of food, but also in the diversion of scientific talent away from innovation and from fields of endeavour totally outside agriculture.

The US Council for Agricultural Science & Technology published a report (No. 87) on the Impact of Government Regulations on the development of chemical pesticides for Agriculture and Forestry in which it is noted that "at least 500 scientist years may have been diverted to regulatory activities at state experimental stations in US during 1972-78". This is a costly diversion of effort to the public.

**Impact on the Environment**

The longer a compound persists the fewer are the sprays needed or the better the control. In other words, the quicker the compound breaks down, the shorter is biological activity on the pest and so, more sprays will be needed or less control will be achieved. The society must decide and implement the decisions through its registration authorities, how much weight to give to the environmentalists. Here Mrs Gandhi's argument at Stockholm in 1972 is relevant. She said "the environment cannot be improved in conditions of poverty, nor can poverty be eradicated without the use of Science & Technology".

For our country, with cash crops as the main exports, we need agrochemicals to protect them and if the cost of production goes up, we can ill afford to accept lower returns. Many of the cheap, cost effective chemicals

are being suspected by regulatory authorities. It should be for the Government to decide in the light of local economic, social, financial and climatic conditions, what agrochemicals they should use. The search for greater safety is utopian under our conditions. Mrs Gandhi has rightly said (*loc cit*). "How can we speak to those who live in villages and slums about keeping the oceans, the rivers and air clean when their own lives are contaminated at the source?" There is no limit for standards of cleanliness. The safety requirements can push the costs beyond what the market can bear. Even then the Industry could still do its job. But at what costs? Who will bear them? The Government or the tax payer? This is not for the Industry to decide.

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