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INDUSTRIAL PRODUCTION AND FORMULATION OF PESTICIDES IN DEVELOPING COUNTRIES

VOLUME I: GENERAL PRINCIPLES AND FORMULATION OF PESTICIDES

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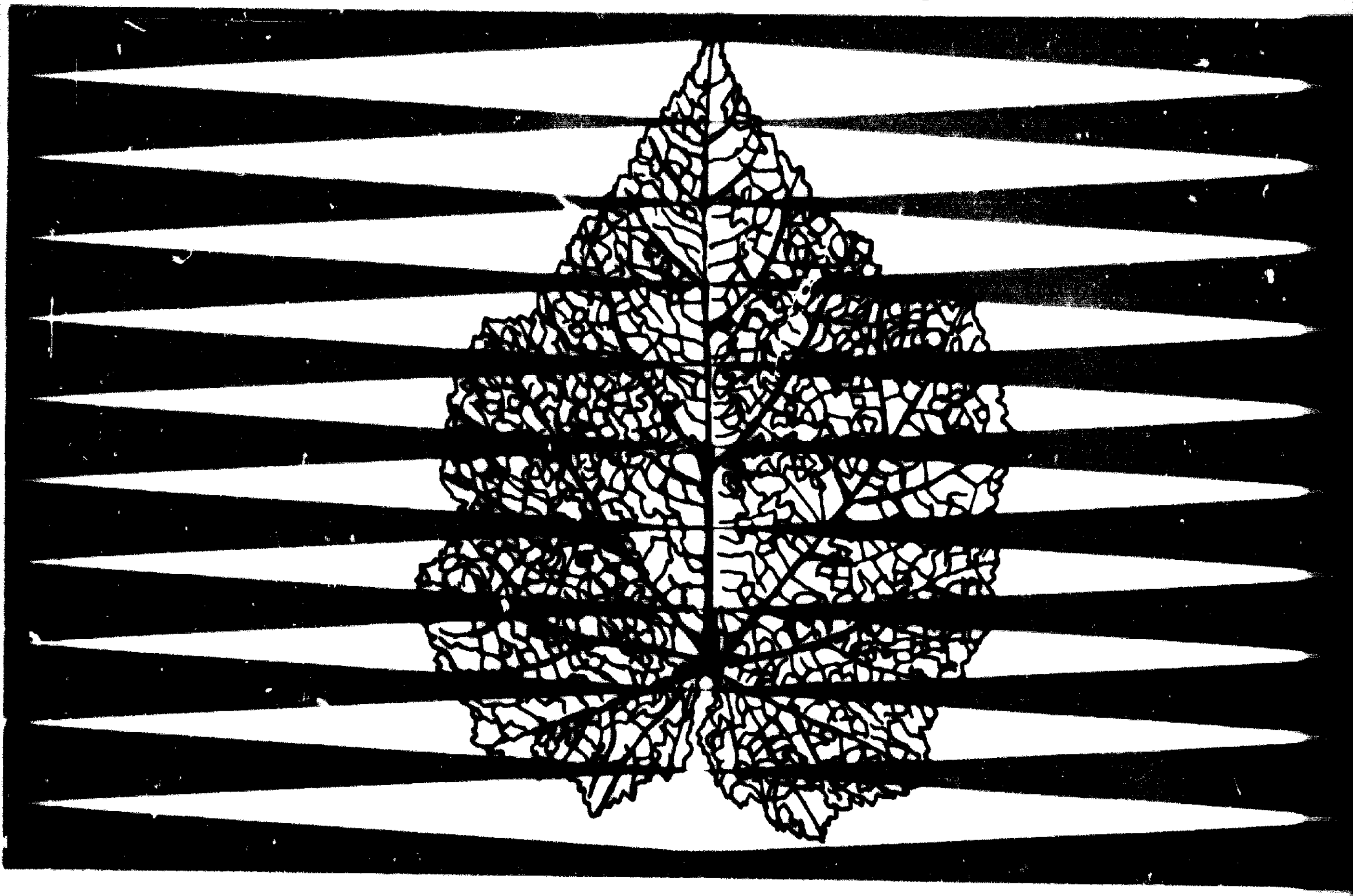

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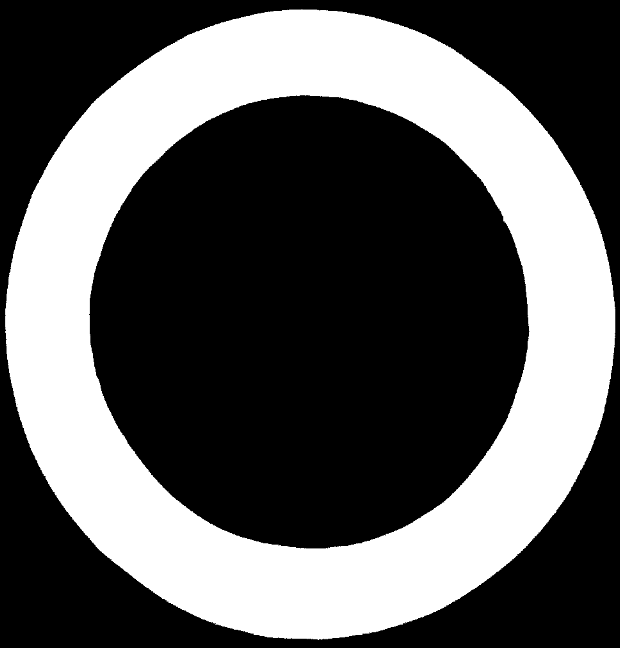

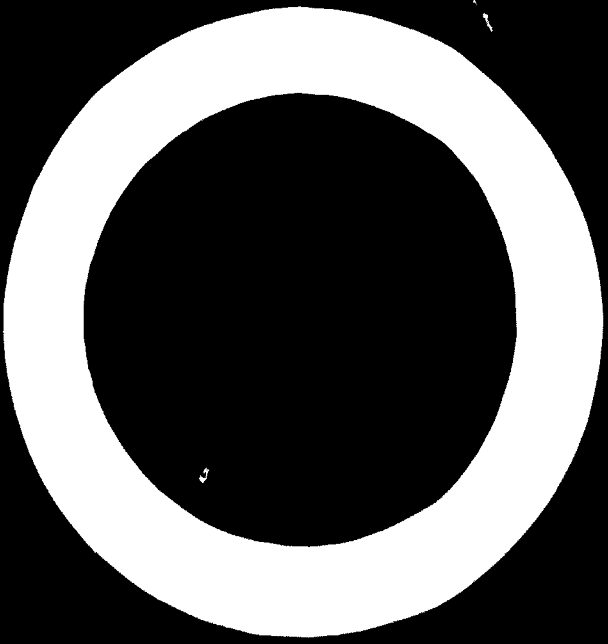

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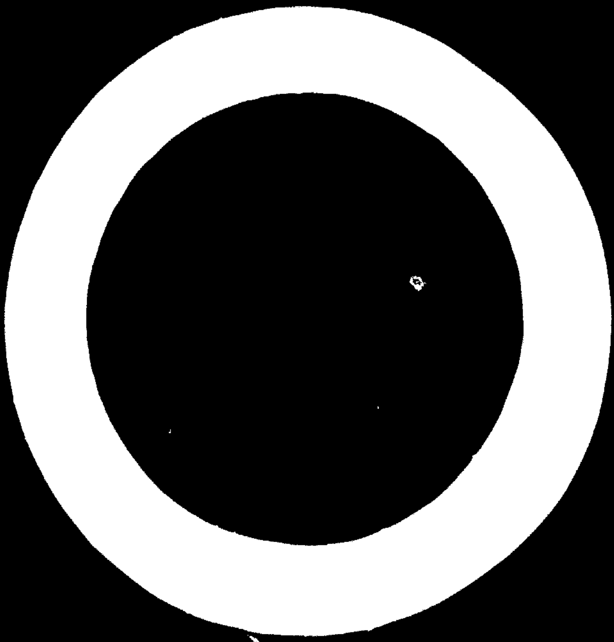

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
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INDUSTRIAL PRODUCTION AND FORMULATION OF PESTICIDES IN DEVELOPING COUNTRIES

VOLUME I:
GENERAL PRINCIPLES AND FORMULATION OF PESTICIDES

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Preface

The emphasis on rationalization and modernization of agriculture in developing countries includes the use of industrial products; e.g. fertilizers, machinery and pesticides. Pesticide production, formulation and use have unique potential for the initiation of new industries in developing countries because they serve both the agricultural and industrial sectors of the economy.

As a part of the over-all commitment to transfer technology from the industrialized countries to developing countries, the United Nations Industrial Development Organization (UNIDO) sponsored group in-plant training programmes on the Industrial Production and Formulation of Pesticides in Developing Countries in Syracuse, New York and at selected industrial locations in the United States in July and August 1969 and 1970.

Information on the chemistry of pesticides is available, but it is usually not in a form suitable for use by industrial chemists responsible for pesticide production and formulating facilities. It is hoped that the present publication, disseminating the Syracuse lectures and discussions on pesticide formulation and production, will serve both educational and practical purposes. Although many of the principles are generally applicable to pesticide production and formulation, the emphasis of the seminar was on such production in developing countries. The installation of multiple-purpose plants has been emphasized in contrast to very large single-product facilities. The use of local raw materials for production of technical grade or formulated pesticides has been stressed wherever possible.

The present volume includes a general discussion of the history of modern, synthetic pesticides and their importance to developing countries. Two chapters are devoted to laboratory analyses of pesticides and the establishment of a pesticide laboratory in a developing country. The principles of pesticide formulations are described in detail; useful suggestions are given on the efficacy and suitability of pesticide formulations. Safety of inherently toxic pesticide chemicals in industrial plants and during shipment are discussed in detail; the importance of safety must not be overlooked when introducing pesticides to farmers and production workers in developing countries. In the concluding chapter, governmental pesticide regulations are discussed on the basis of experience in the United States; these regulations must be appropriately modified for use in other countries.

The interest and co-operation of Mr. I. H. Abdel-Rahman, Executive Director of UNIDO, Mr. N. Beredjick, Director of the UNIDO Pesticides

Training Programmes, Mr. G. Zweig, Director of the Life Sciences Division, Syracuse University Research Corporation and Mr. E. Schoenfeld, Assistant Director, Life Sciences Division, Syracuse University Research Corporation, contributed greatly to the success of these training programmes. Particular note should be taken of the services of Mr. Zweig and Mr. Beredjick, who prepared the manuscript for publication.

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EXPLANATORY NOTES

Dollars ($) refer to United States dollars.

All tons are short tons.

All gallons are United States gallons.

Dates divided by a hyphen (e.g. 1955–1963) indicate the full period involved, including the beginning and end years.

The term "billion" designates a thousand million.

Three dots (. . .) in a table indicate that data are not available.

Abbreviations

cm = centimetre
cp = centipoise
ft = foot
g = gram
gal = gallon
ha = hectare
in = inch
kg = kilogram
l = litre
ml = millilitre
µm = micron
nm = millimicron (nanometre)
ppm = parts per million
rpm = revolutions per minute

Equivalents

1 acre = 0.4 ha
1 dram = 1.7 g
1 US gallon = 3.8 litres
1 pound (lb) = 0.45 kg
1 hectare (ha) = 2.471 acres

Organizations

United Nations

FAO	Food and Agriculture Organization
ILO	International Labour Organisation
WHO	World Health Organization

United States Government

FDA	Food and Drug Administration
USDA	United States Department of Agriculture
USDT	United States Department of Transportation

1. THE IMPORTANCE OF PESTICIDES IN DEVELOPING COUNTRIES

*by Gunter Zweig**

Jonathan Swift wrote, more than two centuries ago, in *Gulliver's Travels*, "that whoever could make two ears of corn or two blades of grass to grow upon a spot of ground where only one grew before, would deserve better of mankind and do more essential service to his country than the whole race of politicians put together". The proverbial ten plagues quoted in the Bible include locusts, grasshoppers, vermin, lice, rodents and the death of the first-born, probably due to a highly infectious bacterial disease. The plagues may have never occurred if the ancient people had known something of modern pest and disease control. Yet, even today in the twentieth century, an agricultural scientist engaged in crop protection (there is not even a name for such a profession) must in fact be a chemist, entomologist, plant physiologist, political scientist, economist and a systems-oriented generalist.

Before discussing pesticides in developing countries, it is essential to take a summary glance at the environment in which pesticides—e.g. herbicides, insecticides, fungicides and rodenticides—are expected to operate beneficially. Although pesticides are the main subject, chemical pest control cannot be isolated from other factors which include plant breeding, fertilizers, economics, and social and political processes.

Wortman[1] has introduced the concept of a crop production equation as a product of variables such as plant variety, fertilizer, soil condition, water, climate, distribution, and pest and weed control. The property of his equation is that if any one factor is optimum, the total product increases, and conversely if a single multiplier is zero, the total yield is zero. Thus, no water, the yield is zero; no weed or pest control, the yield approaches zero and so on. Wortman implies that successful agriculture is systematic agriculture. The pesticide factor of the crop production equation will be discussed with reference to the future of pesticides in developing countries as it affects adequate food production in an increasing population.

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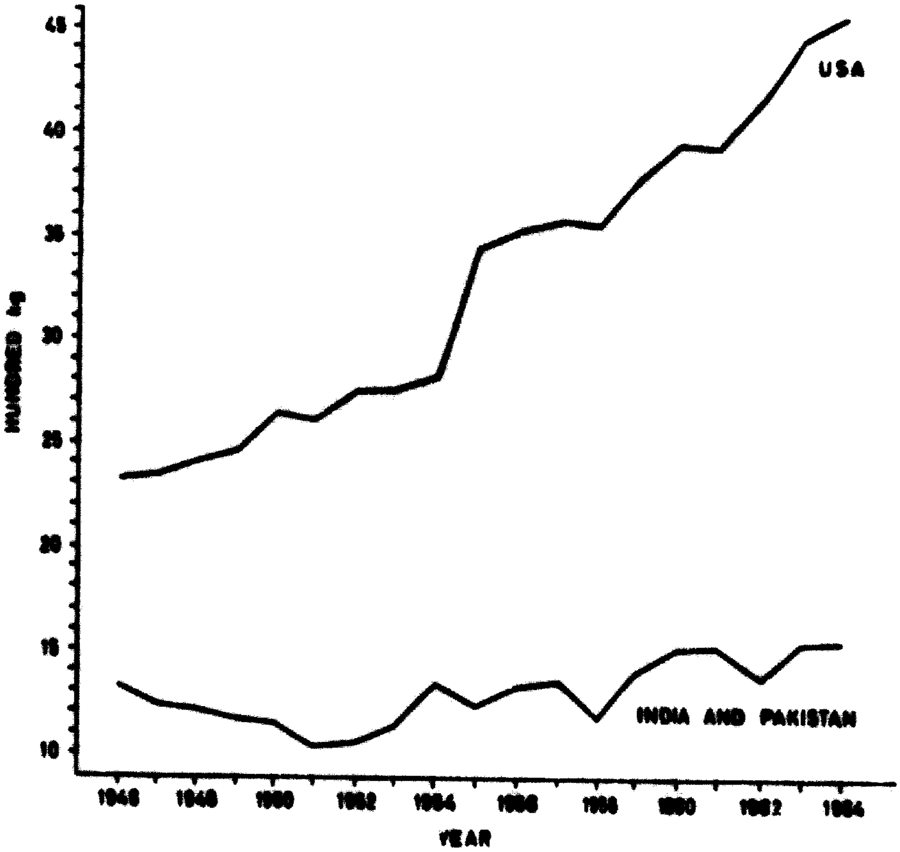
* Director, Life Sciences Division, Syracuse University Research Corporation, Syracuse, New York.

[1] Wortman, S. (1967) "The crop production equation", Lecture at Annual Meeting of the Weed Society of America, Washington, D.C.

FEEDING THE WORLD'S POPULATION

Based on the latest demographic figures available but not taking into account birth control methods, the world's population will increase from 3.3 billion in 1960 to an estimated 6.4 billion in the year 2000—a doubling of the world's population in about 40 years! According to a 1963 survey of the Food and Agriculture Organization (FAO), the world's food supplies must be increased more than 35 per cent by 1975 merely to sustain the unsatisfactory present level of nutrition. With a reasonable improvement in diet, this figure will have to be raised to 50 per cent for the entire world or 80 per cent in the developing countries. By the year 2000 these countries will have to quadruple the volume of their current food production.

Figure 1. Rice yield/ha in India, Pakistan and United States



Source: H. H. Cramer, *Plant Protection and World Crop Production*, Spring, 1967, Farbenfabriken Bayer AG, Leverkusen.

It is an obvious suggestion that modern pest control and chemical weed control might double the world's food supply without changing any other factors of farming. This is illustrated by examining the following estimated losses of agricultural crops grown in the United States due to insect pests and plant disease:

Year	*Million dollars*
1937	789
1954	3,980
1965	6,936

The apparent increase in loss (excluding that due to weed infestation) is explained by an enormous increase in yield per acre, while the percentage of loss due to insects and diseases is constant. Thus in the United States since 1939, the production of wheat, maize, rice and cotton per unit area has increased by 75 to 115 per cent.

The use of modern agricultural methods has markedly increased crop yields. As an example, figure 1 shows a steady increase in rice production per unit area in the United States after the introduction of better agricultural methods during the last twenty years. During this period, the low productivity in India and Pakistan has remained almost constant.

INCREASING AGRICULTURAL PRODUCTIVITY

It may be argued that increased agricultural productivity may create greater problems in countries where widespread unemployment already exists. The argument follows the rationale that gainful employment must be provided for the greatest number of people, even with a resulting diseconomy.

Industrialized countries have experienced the migration of farm workers to the cities after the introduction of improved agricultural practices. However, the displacement of the rural population is not solely responsible for contemporary social and economic problems. The lack of adequate industrial retraining programmes for all unskilled farm labourers who migrate to the cities is another factor.

The developing countries will undoubtedly face even greater problems when outdated farming methods are changed and a large number of the rural population are forced to seek industrial employment. This is a strong argument for agricultural chemical manufacturers from the industrialized countries to build fertilizer and pesticide factories in the developing countries rather than only to export the chemicals.

INTEGRATED AGRICULTURE

As stated earlier, the pesticide market must grow at a rate commensurate with the growth of other factors affecting agricultural productivity. Millikan and Hapgood[2] list the following physical input factors that control agricultural development: fertilizers, pesticides, animals, tools and fuel. In terms of Wortman's yield equation,[3] these factors are important. Failure to optimize any of the

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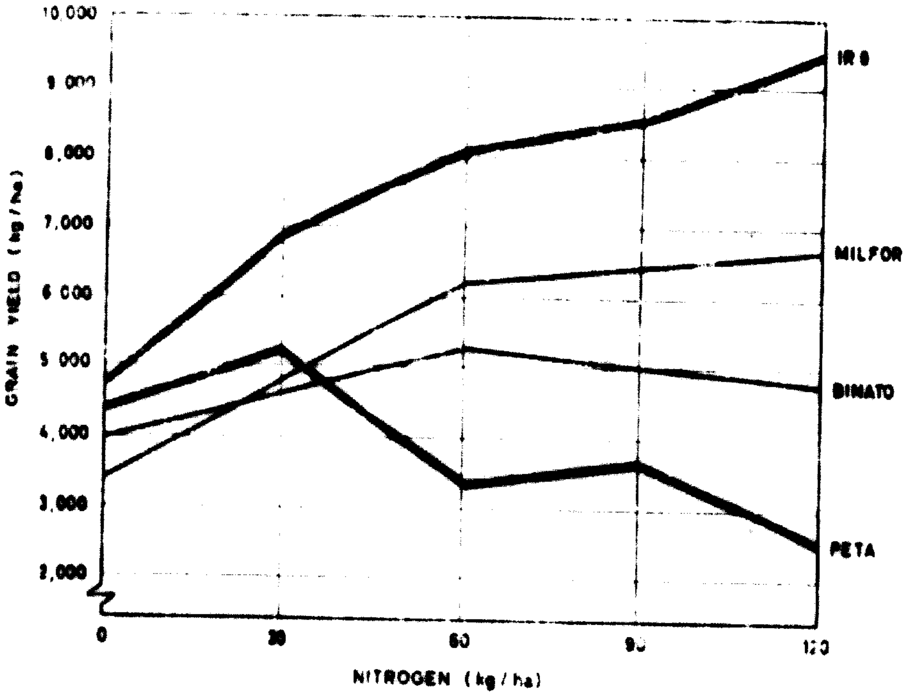
[2] Millikan, M. F. and D. Hapgood (1967) *No Easy Harvest*, Little, Brown & Co., Boston.
[3] Wortman, S., *op. cit.*

factors means limited success in development. Permitting one factor to become zero—e.g. use of a fertilizer unsuited to the land or the plant variety—means substantially zero yield.

Figure 2. Yield of different rice varieties after the use of nitrogen fertilizer



Source: "Toward the Conquest of Hunger", The Rockefeller Foundation, Agricultural Sciences Progress Report, 1965—1966.

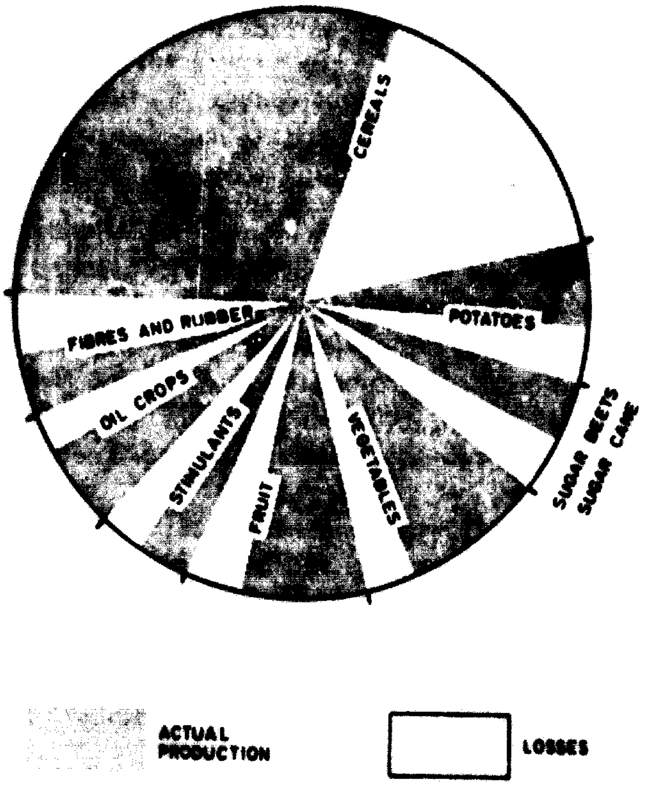
Figure 2 illustrates this point. Peta is a variety of rice long favoured because of resistance to certain diseases. It shows little response (in fact, a negative response) to chemical fertilizers, while the newly developed variety IR-8 from the International Rice Research Institute, Los Banos, Philippines, exhibits an excellent response to the addition of nitrogen. Although chemical weed control increases the crop yield, the economics in this particular case require a consideration of whether the increased costs are justified by the slightly higher yield. It is also noticeable that IR-8 is quite insect- and disease-resistant. The last point is important in the marketing of pesticides. If other, cheaper and less hazardous crop protection techniques are available, the use of organic pesticides should not be advised. More than twenty years of research at the International Rice Institute were necessary to develop the resistant rice variety. In most cases, there is not sufficient time to wait for an optimum development.

Many of the modern inputs, especially the large quantities of fertilizers, create new problems that traditional methods cannot handle. The new crop varieties give high yields because they use the added nitrogen to obtain increased grain yields without lodging. The nitrogen seems to make the crop (at least rice) more susceptible to fungus (blast), bacteria (blight), virus diseases and insect damage. Furthermore, the nitrogen makes the weeds grow more vigorously and compete more strongly with the crops. Therefore pesticides are necessary inputs to realize the potential yields of the new varieties and to avoid yield losses caused by the various pests.

THE ECONOMICS OF PEST CONTROL

The market for pesticides is very implicit in the integrated approach to agricultural production. The potential, global market for pesticides would be very large if the demand for pesticides was related to crop damages caused by insect pests and plant diseases. Figure 3 shows the actual production of crops and the estimated losses. Food losses due to pest insects and plant diseases are about one-third of the total production. Not included in this estimate are the loss of grain and seeds during storage due to insects and rodents, and the loss of livestock due to insects and diseases. Agricultural production could be further

Figure 3. The actual production and estimated losses of different groups of crops



Source: H. H. Cramer, *Plant Protection and World Crop Production*, Spring, 1967, Farbenfabriken Bayer AG, Leverkusen.

increased by chemical weed control; the present "loss" due to weeds is difficult to estimate.

> Cramer,[4] however, estimates the following global losses:
> From insect pests, $29.7 billion or 13.8 per cent of potential production;
> From diseases, $24.8 billion or 11.6 per cent of potential production;
> From weeds, $20.4 billion or 9.5 per cent of potential production.

The market for pesticides is thus rooted in agricultural production which currently forgoes some $75 billion or approximately 35 per cent in potential income.

It has been estimated that the total annual loss from insect pests, weeds and diseases is at least $70 billion and probably is closer to $90 billion. Yet the total annual production of insecticides, fungicides and herbicides is only valued at about $1 billion. This 70-to-1 ratio speaks for itself; in terms of human survival, it speaks for the continuing victims of undernourishment (now nearly 2 billion persons).

As Cramer points out, "Application of modern pesticides as routine programmes on all farms would very quickly put an end to most of the shortages in world food supply, at relatively low capital expenditure."[5] For example, an adequate pest control programme that is carefully linked to and co-ordinated with irrigation, fertilization, plant variety and distribution would increase production sufficiently to provide 2 billion people with a daily quantity of food equivalent to 1.4 kg of rice.

A recent survey of the Brazilian pesticide market by Abrahams[6] clearly showed that the use of pesticides fluctuated from year to year and showed no steady increase. Furthermore, the pesticides were used mainly in the well developed state of São Paulo on one major crop (cotton) and at a much lower level on coffee. Only minor quantities of all pesticides used in Brazil were manufactured domestically; most pesticides were imported. The following conclusions are derived from this survey:

> There is a need for the use of pesticides on many crops indigenous to the developing countries and in all regions of these countries.
> The alternatives are importing pesticides or building chemical factories in these countries. The latter development is more desirable from the country's point of view but depends in part on the availability of raw materials and other factors.

The United States export of pesticides increased from more than $173 million in 1966 to more than $195 million in 1967. A large percentage of pesticides

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[4] Cramer, H. H. (1967) *Plant Protection and World Crop Production*, Farbenfabriken Bayer AG, Leverkusen.

[5] *Ibid.*, p. 492.

[6] Abrahams, A. E. (1967) private communication.

produced in the United States, especially those manufactured by non-proprietory technology, could be replaced in many developing countries or regions by locally produced materials.

THE PROBLEMS OF PESTICIDE MARKETS IN DEVELOPING COUNTRIES

The ecology and resistance problems

Intensive agriculture results in multicropping, thicker foliage and denser stands and thus provides year-round luxury for insect pests and diseases. Excessive and indiscriminate use of pesticides has the inherent danger of destroying the ecological balance, killing beneficial insects and increasing the population of other damaging pests.

Since the reproductive cycle of most insects is short, resistant species are quickly developed after the introduction of a new pesticide. The most widely cited example is the common housefly and mosquito in their highly successful counter-attack on DDT. Brown stated in 1961 that "the total number of species with resistant strains has risen since 1945 to the appalling figure of 137... Resistance was about equally divided between plant-feeding insects and mites, and insects or ticks of public health or veterinary importance".[7]

The relative effectiveness of chemicals used for agricultural pest control changed sufficiently in recent years to alert the FAO to the need for intensive study of the problem. In the Report of the First Session of the FAO Working Party, it was noted that since Brown's study the number of resistant species of pest insects had risen to over 200. It is "a sobering indication of the rate of spread and ubiquity of this threat to crop protection".[8]

Further complicating this unhappy situation is the cross-resistance phenomenon. In a 1964 study by Winteringham and Hewlett,[9] a series of resistant groups were bred in which resistance to one chemical meant resistance to all pesticides in the group. Notable examples cited are DDT, lindane, dieldrin, chlordane and other chlorinated pesticides. It is important, therefore, to recommend that growers in the developing countries use pesticides sparingly and only in those cases where other pest control methods are no longer successful.

Pesticides may be poisons

A further danger arises from the basic nature of pesticides. They are poisons, and while much is known about their effect on humans and livestock, there is an inherent danger in the simple presence of such materials in the farmyard.

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[7] Brown, A. W. A. (1961) *Bulletin of the Entomological Society of America*, Vol. 7, p. 7.

[8] Food and Agriculture Organization (1965) *Report of the First Meeting of the FAO Working Party on Pest Resistance to Pesticides*, Rome, PL/1965/18.

[9] Winteringham, F. P. W. and P. S. Hewlett (1964) *Chemistry and Industry*, Vol. 35, pp. 1512--1518.

Illiteracy is common in many developing countries, and the warning on the bag is frequently not read and understood.

Two cases illustrate the inherent danger of some of the most effective and the most poisonous pesticides. On 27 September 1967, in the town of Tijuana, Mexico, just south of San Diego, California, 17 persons died and many others were hospitalized after eating bread in which parathion was found. The insecticide was traced to a container of parathion stored next to bread ingredients in the warehouse. A more tragic accident occurred two months later in a small town in Colombia, where 80 persons died after eating bread contaminated with parathion. The contamination was traced to a one-pint container of pesticide which broke and leaked into flour which stood next to the pesticide. A reader of the *New York Times* wrote to the editor after the accident had occurred and suggested to simply add a coloured dye to the parathion, so that the baker would immediately become suspicious if he saw, say, red flour or blue sugar. Consequently, a directive from the Commissioner of the Food and Drug Administration (FDA) now forbids the storage or transport of any pesticide next to or with food products.

Manufacturers and suppliers of such inherently dangerous substances have a responsibility to take every step possible to protect the user and the general public. Exporters of pesticides must necessarily work directly or indirectly with the governments of other countries to establish the necessary educational programmes which will ensure the safe use of pesticides.

The residue problem

Pesticide residues in foods is a problem because residues are present in minute quantities in almost all crops grown under modern methods. The resistance phenomenon intensifies the problem of residues since the early stages of insect resistance may be overcome by increased use of the pesticide. The FAO Report states, "One obvious effect is an increase of residues of persistent compounds as a result of increased dosage rates. Many problems of undesirable residues in milk, meat and other animal products that have been carefully investigated can be traced to the contamination of an animal feed that is in whole or part made from by-products of processing a root crop, or feeding the non-marketable root crops themselves".[10]

The pesticide manufacturer and user must be aware of legal tolerances in the producer country and in its export market. These tolerances can vary substantially. DDT and other chlorinated pesticides, for example, are under severe attack by toxicologists in many countries including the United States, and there is an active campaign to prohibit the use of these pesticides completely. Yet

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[10] Food and Agriculture Organization, *op. cit.*

DDT is still one of the cheapest, most readily produced and most effective pesticides.

It is remarkable that the threat to human health at low levels has not been established. The banning of DDT seems to have grown out of an emotional reaction rather than an established scientific observation. In countries where technological advances in agriculture have resulted in a level of productivity which permit the use of sophisticated control techniques, the banning of one insecticide may be acceptable. But, it is suggested that in the developing countries with 2 billion starving or nearly starving people, such arbitrary action is a luxury beyond reason.

The sociological problem

Millikan and Hapgood point out that pest control, like irrigation projects, demands a high form of social control: "Many forms of pest control cannot be usefully adopted by a single farmer or even a majority within a community. This is true for combating migratory insects and diseases that spread from one field to the next. In order for the pest to be successfully controlled, each farmer in the area must be convinced or coerced to join the program".[11]

FUTURE DEVELOPMENTS

The problem of increasing food production to keep pace with the world's increasing population and of attempting to meet minimum nutritional standards is so vast that no single industry or no single country can undertake all of the necessary measures. Efforts of the Rockefeller and Ford Foundations in establishing the International Rice Research Institute in the Philippines are laudable. Two pesticide laboratories have been established by FAO in Brazil and in Egypt. They facilitate testing pesticides for specific, regional problems. The industrialized nations of the world have recognized that the way to help developing countries is first to feed them by supplying food, but secondly, and much more important, giving them tools and know-how so that these countries will eventually be able to feed themselves. Thus foreign experts have been sent on special missions; e.g. to the Philippines to develop chemical control methods against weed infestation in rice fields and to Brazil to survey the pesticide industry and the need for pest control. The latter mission was sponsored by the FAO.

The 1967 conference on food safety held in Mayaguez, Puerto Rico, was sponsored by the United States Public Health Service and was designed for food experts from North and South America. Besides bacterial and toxic contamination of foods, pesticide residues in agricultural crops were discussed. Many

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[11] Millikan and Hapgood, *op. cit.* p. 49.

of the delegates from South America remarked that minute pesticide residues in foodstuffs were really the "luxurious" concern of the overfed nations, and that the largest problem today was the feeding of an undernourished population.

Study of specific problems

What can the agricultural chemical industry of industrialized countries do to help developing countries in the introduction of modern pest control methods? It would be a mistake for a chemical company to export pesticide chemicals and know-how which might be applicable to the United States but may have no relation to the developing countries which are situated mostly in the tropical zone. Agricultural experts from the Union of Soviet Socialist Republics, the United States and Western Europe should study in detail the particular pest insects, plant diseases and economic and sociological factors of each developing country or region. Only then can the needs of a particular country or region be determined. Thus, it is most imperative that pesticides are not exported indiscriminately.

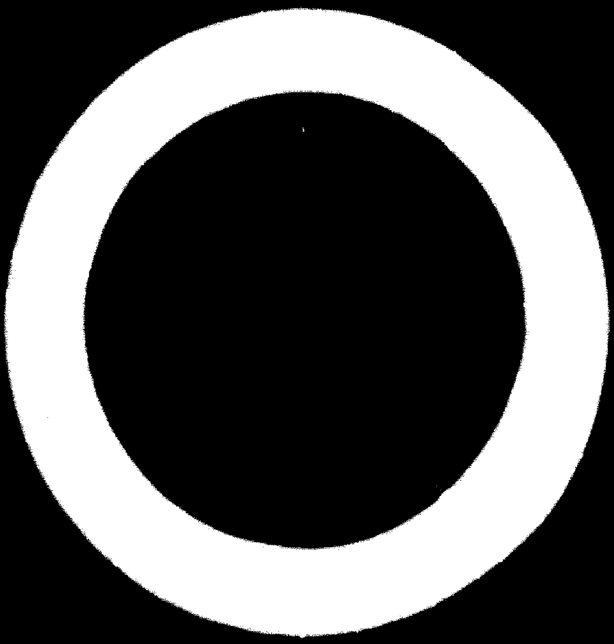
Development of specific pesticides

Once a determination has been made of a particular pest control need in a developing country or region, specific pesticides must be developed to combat the particular infestation or disease. Normally, screening of new pesticide chemicals by industry is restricted to those compounds which would have the greatest domestic market potential. In the United States, important crops are maize, soybeans, wheat and cotton. Rice is by far the largest crop in the Far East, and coffee is an important crop in South America. Thus, it is most important for the pesticide industry in the industrialized countries not to forget the crops, pest insects and diseases in other countries. To encourage a broader spectrum of pesticide chemical development, institutes like the International Rice Research Institute, the FAO pesticide laboratories and many experimental agricultural stations throughout the world are most anxious to test new compounds and to make appropriate recommendations. Although this testing service is in most cases voluntary, the establishment of research grants or fellowships by industry might facilitate the work.

Import versus domestic production of pesticides in developing countries

The decision to import or to produce pesticides locally should be decided on an individual basis. What are the raw materials situation and the labour market? What is the industrial climate? How urgent is the need for pesticides? It would appear that production of basic pesticides like DDT and parathion in each country is preferable to importing pesticides since any new industry created in the countries may help to alleviate the unemployment created by mechanized farming.

In conclusion it must be stressed that a vast potential market for the production of all kinds of pesticides exists in developing countries. The development of this industry represents not only an excellent return to investors but a great humanitarian act by helping to feed the hungry, the undernourished and the starving people of the world.



2. INTERNATIONAL ASPECTS OF PESTICIDES

*by Kenneth C. Walker**

There are many approaches to the subject of international aspects of pesticides. One of the major aspects could well be the production, demand and usage of pesticides on an international scale. This approach could be expanded to include the projections of pesticide usage such as from insecticides to herbicides as the insect problems are brought more under control and the problems of weed control become more acute.

Another main approach to the subject could be the potential impact that the usage of pesticides in any one country could have on the health and well-being of its population. Consideration of the health aspects of pesticide usage is not limited to the particular country but quickly encompasses other countries when the producing country becomes engaged in the export of pesticide-protected commodities. Both of the above approaches will be touched upon in presenting the information which follows.

PRODUCTION AND USE OF PESTICIDES

According to the 1968 *Pesticide Review*, the production of pesticides continues to increase in proportion to the increased usage in the United States and the increased export demand. Within the United States, certain government rules and regulations influence the amount of detail that can be presented in the publication of production figures. The main influence is exerted by the regulation that protects the production information of companies that are either the major supplier or the sole supplier of a particular commodity. This rule covers the situation where there are not more than three suppliers and one of the three companies produces the bulk of the chemical. Under these conditions, the production figures of the company or companies are privileged information and as such cannot be revealed to the general public. For this reason, certain pesticides have been grouped in the presentation of the production data. For example the term "aldrin-toxaphene group" is used, although it is recognized that the pesticides included in this group (aldrin, chlordane, dieldrin, heptachlor, strobane and toxaphene) are not necessarily closely related from a chemical

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* **Assistant to Deputy Administrator, Agricultural Research Service, United States Department of Agriculture, Washington, D.C.**

standpoint. However, these chemicals are produced by single companies and the production figures are privileged information.

The production of synthetic organic pesticides in the United States increased more than 37 per cent between 1963 and 1967; it ranged from 2.5 per cent in 1964 to 15.5 per cent in 1966. The dollar value of pesticide exports increased more than 61 per cent between 1963 and 1967.

The production and sales of herbicides have increased at a faster rate than those of insecticides. Herbicide sales have risen 27 per cent in value since 1963, which is more than double the rate for insecticides. The herbicide share of the market has continued to grow at the expense of the other groups.

It is believed that the United States produces from 50 to 75 per cent of all pesticides manufactured in the world. Exact figures on pesticide production on a worldwide basis are not obtainable for a variety of reasons. As indicated above, there are certain rules and regulations within the United States that provide protection for manufacturers. Undoubtedly there are similar constraints applied in other countries.

Judging from the United States export market, the demand for pesticides in other countries is increasing to meet the world's food needs. It is anticipated that other countries will develop additional capacity or increase existing capacity to produce these chemicals. As this development takes place, the proportion of the total pesticide production from the United States will decrease. Insecticides and fungicides will probably dominate the herbicides in the world market. However, advances in the mechanization of agriculture will continue to promote the growth of the market for herbicides.

Data prepared by the Business and Defense Services Administration, United States Department of Commerce, indicate that the production of DDT in the United States in 1968 increased 33 per cent over the 103 million pounds produced in 1967. Of the 138 million pounds of DDT produced in 1968, the export market accounted for 79 per cent of the sales. Exports of all pesticides in 1968 were valued at $241.5 million, which is an increase of 23.4 per cent over the 1967 market.

A large complex of pest species share man's requisite for food. They include viruses, bacteria, fungi, protozoa, nematodes, insects, birds and rodents. Weeds do not consume food directly but reduce food production through competition with plants for nutrients, water and sunlight. The direct loss of food as a result of pests has been impossible to determine accurately, but it is known to be large, and the minimum estimates of world losses range from 20 to 30 per cent of the total food produced. In planning for increased agricultural production, recognition must be given to the extensive and convincing evidence that pest problems are intensified as yields are increased through the use of more fertilizer, better seed, better water management and other improved production practices. If the maximum benefits are to be obtained from a system employing these production inputs, effective crop protection methods must be a part of the system.

An example of the importance of crop protection comes from rice production. Formerly, weed control was obtained by maintaining a 6- to 8-inch (15.2 to 20.3 cm) depth of water. The development of selective herbicides has made it possible to control the weeds without this expensive water management technique. With the proper use of herbicides it is now possible to lower the water level to 2 inches (5.1 cm) and use some of the shorter stemmed rice varieties that respond more effectively to higher levels of fertilization (see chapter 1).

The use of chemical pesticides increases very rapidly as plant production is increased. *The 1963 FAO Production Yearbook* shows pesticide use and the yields of major crops for seven areas or countries as the table below indicates. There is excellent correlation between pesticide use and yields.

AREAS AND COUNTRIES IN ORDER OF PESTICIDE USE PER HA AND OF MAJOR CROP YIELDS

Area or country	*Pesticide (g/ha)*	*Yield (kg/ha)*
Japan	10,790	5,480
Europe	1,870	3,430
United States	1,490	2,600
Latin America	220	1,970
Oceania	198	1,570
India	149	820
Africa	127	1,210

PESTICIDES AND WORLD HEALTH

In recent years the presence in food of pesticide residues has received increasing attention, especially in Europe and the United States. The public, including government officials, farmers, the agricultural industry, scientists of varying disciplines and the consumer, has participated in numerous deliberations on this subject. Concern has been expressed that pesticide residues are a threat to the public health and that they may adversely affect the quality of food. It has been claimed that food crops can be grown without using pesticides; that a hazard to wildlife is created by their use, and that pesticides have upset "the balance of nature". Reference is often made to the "hazard" of using pesticides and the "toxicity" of these materials. Hazard and toxicity when coupled with the word chemical seem to create a subconscious fear in the minds of the general public, which lacks the scientific training and basic knowledge to make a calm appraisal of the subject.

Pesticides, like other elements that influence man's environment today, have both real values and potential dangers. It is unfortunate that in no phase of man's existence can all risks be eliminated. This is true of chemicals as it is of atomic energy, the automobile and even the many aspects of every-day living. The challenge in the safe use of pesticides is to ensure an adequate supply of wholesome and nutritious food, provide sanitary living conditions and freedom from pest-borne diseases, and at the same time, prevent hazards to the health of man, beneficial animals and other segments of the environment.

The health of humans and of beneficial animals and the general ecological balance are of great concern to all. When pesticides are used, every effort must be made to avoid serious impacts on fish, wildlife and other segments of the environment. Moreover, the entry of pesticides into the food chain of fish and wildlife and the concentration of these pesticides in certain organs are important matters which must receive thorough and intensive investigation.

Since almost everyone uses pesticides of one sort or another, the responsibility for their safe use should be shared by all. The pesticide industry has a grave responsibility for developing and producing chemicals that are safe and useful for the public. Professional workers in agriculture, public health and private medicine have a responsibility for signalling danger when any aspect of man's changing environment poses a threat to human health. Extreme care must continue to be used in recommending and regulating the most efficient and the safest possible methods of pest control.

The continued and widespread use of pesticides is essential to the production and protection of increasing yields of agricultural products and to the control of many diseases of man and animals. Experience has shown that various essential precautions must be carefully followed during the course of pesticide manufacture, distribution and use. In some countries, regulations to promote safe and effective use are in effect; in other countries, regulations have been introduced or are under consideration.

The control of risks to which workers or others may be exposed during the process of manufacture and formulation of pesticides presents problems, many of which are common to those relating to the manufacture of other chemical products (see chapter 8). Similarly, the protection of employees and other persons who may be exposed during the course of the application of pesticides in the field raises special problems. In many countries these risks are covered by legislation which relates specifically to the respective fields of activity.

The Director-General of FAO in July 1963 established a working party of experts on the official control of pesticides. It reviewed the existing pesticide control schemes in approximately 25 countries. The report of the working party included recommendations for provisions which should be incorporated in comprehensive pesticide legislation of any country for the guidance of the governments. The provisions in the form of guide-lines have been reviewed by interested national and international organizations and have been discussed with representatives of the World Health Organization (WHO) and the International Labour Organisation (ILO).

The guide-lines presented by the FAO Working Party will aid in regulating the safe and effective use of pesticides insofar as this can be done by registration of pesticides for marketing and sale. The problem of registration and regulation of pesticides during their manufacture, formulation, transportation, distribution, sale and use is not a matter with international aspects unless one or more of these activities become involved in international commerce. Pesticides may be manufactured and formulated in one country and then transported, distributed, sold and used in another country. When these conditions exist, the many phases of the international aspects of pesticides come into play. The guide-lines proposed by the FAO Working Party and published jointly by FAO and WHO are not all-inclusive, but they do contain suggestions on many fundamental factors that are involved when pesticides are produced, transported and sold in international commerce.

PESTICIDE RESIDUES

Another aspect of pesticides in international commerce concerns the residues of the pesticides or of their metabolites on or in agricultural commodities shipped from one country to another. Like the process of registration and regulation of pesticides, the establishment and enforcement of pesticide residue tolerances varies from country to country. In some countries official residue tolerances have not been established; in other countries tolerances are established and have the force of legal regulations. They can be enforced with appropriate penalties when violated. In recent years, the number of countries that have established residue tolerances for certain pesticides on or in raw agricultural commodities has increased. It appears reasonable to expect that there will be further increases in the number of countries that will establish residue tolerance regulations. The right of each country to establish its own food laws cannot be questioned. However, the large and ever-increasing volume of international trade in foods would deem it desirable that reasonably uniform food legislation and tolerances be established.

Because the pesticide residue problem is of international concern, the different approaches adopted by various governments indicate an urgent need for the international exchange of views and experience as well as technical information. During recent years, efforts in this direction have been initiated by United Nations agencies and other international groups.

Activities of FAO and WHO

At a joint meeting in 1961 of the FAO Panel of Experts on the Use of Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues, it was recommended that studies be undertaken to evaluate the consumer hazard arising from the use of pesticides. Toxicological and other pertinent data on those pesticides known to leave residues in food, even when used in accordance with good agricultural practices, were to be examined and the conclusions made known.

The FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues held a joint meeting in Geneva in 1963 and issued a report dealing with 37 pesticides and suggested acceptable daily intakes for 15 of them. The same substances were re-evaluated at a subsequent joint meeting in Rome in 1965. In addition, other pesticides were evaluated and the results of the deliberations reported. These reports, which concerned themselves primarily with the recommendations of acceptable daily intakes, were then considered by the FAO Working Party on Pesticide Residues, which is a subgroup of the FAO Committee on Pesticides in Agriculture, with the aim of recommending tolerances and appropriate methods of analysis for certain pesticides used on cereals.

The purpose and terms of reference of the FAO Working Party on Pesticide Residues are to advise and assist the Director-General of FAO on all matters related to pesticide residues with particular reference to:

Determination of the availability of residue data and the collection of these data;

Evaluation of data and proposal of pesticide residue tolerances;

Evaluation of analytical methods and recommendations of acceptable methods of analysis;

Recommendations designed to initiate, stimulate and co-ordinate the necessary research as indicated by their studies.

The WHO Expert Committee on Pesticide Residues is responsible for advising the Director-General of WHO on all matters related to pesticide residues with particular reference to:

Review of toxicological and related data on certain pesticide residues;

Proposal of, where possible, acceptable daily intakes for man for those pesticide residues that have been reviewed;

Recommendations designed to initiate, stimulate and co-ordinate necessary research.

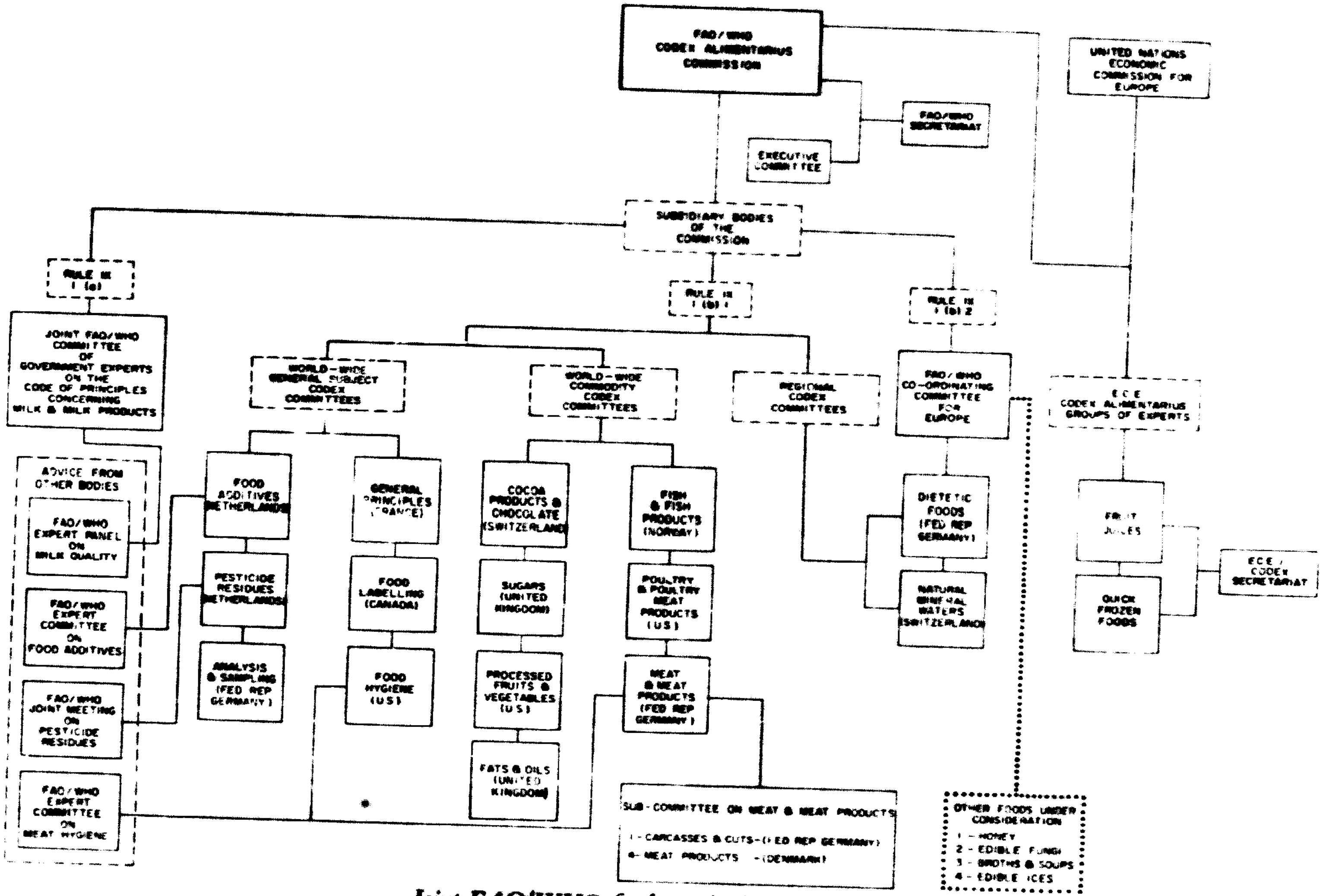
Codex Committee on Pesticide Residues

The recommendations of the FAO Working Party on Pesticide Residues were presented to the member governments of another international organization, the Codex Committee on Pesticide Residues. In 1962, the Codex Alimentarius Commission was established to implement the Joint FAO/WHO Food Standards Programme with the organization outlined in the figure. The purpose of the programme is to protect the health of consumers and to ensure fair practices in the food trade, to promote co-ordination of all food standards work undertaken by international, governmental and non-governmental organizations, to determine priorities and initiate and guide the preparation of draft standards through and with the aid of appropriate organizations, to finalize standards and after acceptance by governments, to publish them in Codex Alimentarius either as regional or world-wide standards.

The Codex Alimentarius Commission is comprised of the members and associate members of FAO and WHO which have notified the Director-General of FAO or WHO of their wish to be considered as members. As of 1 June 1968, 53 countries had become members of the Commission. The members of the Commission and of national codex contract points are given in annex 1.

The Commission has established seventeen subsidiary bodies of which two deal with general policy and co-ordination, six with subject matters relevant to the work of all commodity committees and nine with specific groups of foods. The Codex Committee on Pesticide Residues is one of the six committees with subject matter relevant to the work of all commodity committees.

This Committee is responsible for proposing international tolerances for pesticide residues in specific foods. A further responsibility is the preparation of a list of priorities of those pesticide residues found in food commodities entering



Joint FAO/WHO food standards programme international trade for toxicological evaluation by the WHO Expert Committee on Pesticide Residues and examination by the FAO Working Party on Pesticides. The list of priorities is forwarded to the two expert committees for consideration and is not binding on them. The expert committees establish their own lists of pesticides to be investigated. The committees serve as scientific advisers to the Codex Committee on Pesticide Residues.

There are ten specified steps or procedures which must be followed in order to establish an international tolerance. An outline of the procedure for the elaboration of world wide Codex standards is given in annex 2. At the third and sixth steps the individual country has an opportunity to comment on the proposed tolerance. At the ninth step the individual government has the opportunity to accept or reject a proposed international tolerance. At present, proposed international tolerances are at nearly all stages of consideration from the first stage (a decision to request a tolerance), to the ninth stage (the governments can decide to accept or to reject the proposed tolerance level). No international tolerances for pesticide residues have been finalized to the point that they are ready for publication.

To date, the bulk of the data that have been available to the FAO and WHO committees for evaluation has been generated in countries with the most experience in the use of pesticides because these countries could provide the facilities and personnel for the determination of toxicological, pharmacological and pathological properties of some pesticides. In addition, data have been accumulated on the chemical and entomological aspects of pest control agents and on residues resulting from good agricultural practices.

In considering the use of pesticides there is general agreement among toxicologists and other health experts that the level of human exposure should be maintained as low as possible. This is simply good public-health policy. Likewise, there is general agreement that pesticides are useful and essential in helping to provide a supply of food for an ever-expanding world population. From these general agreements arises one of the major problems in the development of international pesticide residue tolerances. The level of pesticides in food must be kept at a minimum and, on the other hand, food supplies must be protected by pesticides to provide basic nutrition requirements; pesticide levels must be high enough to provide this protection. It is not always possible to accommodate the three factors to the same degree.

The establishment of international tolerances is further complicated by the requirements that pesticides be used within the concept of good agricultural practices, which is a rather ill-defined term. Good agricultural practices vary between countries and even between different geographical locations within one country. For example, warm semi-tropical countries with long growing seasons may require more frequent applications of a pesticide than a cooler area. Differences in rainfall between countries or within a country may well affect the use of pesticides such as fungicides. Local conditions of availability of labour can have an influence on the use of herbicides. These and many other factors are all part of good agricultural practices. There is little if any reason to believe that agricultural practices can be standardized to an extent sufficient to warrant their consideration as a part of establishing international tolerances based mainly on the protection of human health.

International tolerances for pesticide residues must be based on the highest tolerance required under good agricultural practices by any of the exporting countries. The established figure must be at such a level that the ingested pesticide residues resulting from these and other uses of the particular pesticide do not exceed the actual daily intake (ADI) established by WHO. There can be no exception to this rule regarding ingested residues. Any international tolerance recommended to member governments by Codex Alimentarius must recognize the needs of the exporting country provided that country has demonstrated the need for the tolerance under good agricultural practices and provided the tolerance level has been established by the Joint FAO/WHO Expert Committee.

To actually determine if the consumer is at risk, it is necessary that the ADI of the pesticide be determined. This type of determination has been done in the measurement of the "dinner plant" or "market basket" samples conducted in the United States and a few other countries. With one exception, the results of these studies have indicated that the actual ADI was well below the permitted daily level. In the one exception, immediate changes in the patterns of pesticide use reduced the ADI of the pesticide to a level well below the calculated permitted daily level. This type of investigation is time-consuming and expensive but adequately justified in establishing the safety of pesticide residue control procedures.

The Director-General of FAO called attention to the following recommendation in the 1966 Joint Report of the FAO Working Party on Pesticide Residues and the WHO Expert Committee on Pesticide Residues:

> In the course of its work, the FAO Working Party on Pesticide Residues frequently encountered gaps in information on world patterns of pesticide use, residues resulting from experimental programmes, residues found in commerce, and losses of residue during storage and food processing.
>
> The results of residue analysis of total diet studies have also been particularly useful in assessing the probable actual intake of pesticide residues by man. The Director-General of FAO is required to ask member governments to obtain these data and to make them available to FAO.

Thus, until the above gaps in information are filled, the decisions on tolerance levels can only be based on the data presently available. The developing countries can help to provide this badly needed information through appropriate organizations and official governmental bodies so that the purpose of Codex Alimentarius as stated in the general principles may be fully realized:

> Codex Alimentarius is a collection of internationally adopted food standards presented in a uniform manner. These food standards aim at protecting consumer's health and ensuring fair practices in the food trade. Their publication is intended to guide and promote the elaboration and establishment of definitions and requirements for foods, to assist in their harmonization and in so doing to facilitate international trade.

3. HISTORY OF PESTICIDES

*by Herbert Haller**

From time immemorial, man has been in a continual battle with pests, which compete for his food supply, damage his possessions and attack his forests, his livestock and himself. Pests include injurious insects, plant diseases, weeds, nematodes and rodents. Some insects transmit plant diseases, destroy vegetables, fruits and cereals, and damage livestock. Others infest grains in storage and dried fruits during and after the drying process. Clothes moths, carpet beetles and termites ruin clothing and damage houses. In addition to the destruction caused by their voracious appetites, insects harbour and transmit some of the most serious diseases of humans and animals. Some of the world's most dreaded diseases, such as malaria, epidemic typhus, bubonic plague and African sleeping sickness, are insect-borne. Plant diseases caused by fungi, bacteria and viruses interfere with crop productivity. Weeds compete aggressively with vegetables, cereals, forage and similar crops and sometimes ruin large range areas. Nematodes and rodents similarly are destructive to man's agricultural resources. National frontiers have no meaning for these enemies of mankind. The problem of their destruction is of prime importance for the well-being of all countries; their necessary control requires international co-operation.

The control of agricultural pests may be accomplished in several ways—by biological methods, that is the use of parasites and predators; by planting resistant varieties of crops, by cultural practices such as crop rotation, by the proper timing of plowing and planting, and by the use of chemicals. From earliest times chemicals have played an important role. Such chemicals are now designated by the comprehensive or generic term pesticides. The term includes insecticides, fungicides, herbicides, nematicides and rodenticides, as well as plant defoliants and desiccants.

INSECTICIDES

A few of the present-day insecticides have been used for many centuries. However, until about 100 years ago, most of the early uses were sporadic and were not part of a continuous effort. Early suggestions for protecting plants from insect attack included superstitions that cultivating practices should be

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carried out during certain phases of the moon. A practice in the United States that is still carried out in some areas is to plant root crops (e.g. potatoes) in the dark of the moon.

Arsenic compounds

Among the early uses of insecticides were baits containing arsenic for grasshopper (locust) control. Records indicate that the Chinese employed arsenic sulphides to control insects on garden plants as early as 900 A.D. The burning of sulphur has long been employed to check infestations in stored products and as a disinfectant.

About 1860, several developments made agriculturalists in the United States more conscious of the need for insect control. Intensive agriculture resulted in multicropping with thicker foliage, and denser stands of plants provided year round feeding for insect pests and the spread of plant diseases. Probably the most urgent development was the sudden appearance of the Colorado potato beetle as an economic problem. This insect is native to the eastern slopes of the Rocky Mountains of western United States where it had previously fed on wild solanaceous plants. It found the potato a particularly acceptable food when the westward spread of potato culture brought that important crop within its reach. Paris green (copper acetoarsenite) which was being used as a paint pigment was found to be highly effective against the beetle, and by 1870 it was used widely as an agricultural insecticide. Within a few years London purple (a mixture of calcium arsenite, calcium arsenate and miscellaneous materials including small amounts of dye) became available and from 1880 to 1900 these two chemicals were the most commonly used insecticides. Paris green was used all over the world where oiling was formerly the only chemical means in malaria-control operations. Paris green burns foliage and is therefore an example of the requirement that the formulation must not be phytotoxic. Moreover, Paris green is a heavy powder that settles rapidly from suspensions and has poor adhesive properties. Thus the need for insecticides having better physical and chemical properties was evident. Emphasis at that time was on insecticides containing arsenic, and in 1892 lead arsenate was prepared for the first time.

The superiority of lead arsenate over other insecticides was soon demonstrated, and by 1910 it had largely replaced Paris green and London purple. Until displaced by DDT and parathion shortly after the end of the Second World War, lead arsenate was more extensively used against orchard pests than any other insecticide. In 1920, about 30 million pounds were used and by 1945 the annual consumption had increased to about 80 million pounds.

Calcium arsenate is a complex mixture of several calcium arsenates and an excess of calcium hydroxide. It became available commercially in the United States about 1919, although it had been first prepared ten years earlier. Because calcium hydroxide was less expensive than lead arsenate, it soon found extensive use as a dust on cotton for boll-weevil control frequently in combination with sulphur. Although effective against a number of field and horticultural insect pests, calcium arsenate could not be used on apples, peaches, beans and other crops because of its burning effect on the fruit and foliage. By 1947, approximately 48 million pounds of calcium arsenate were used in American agriculture. The following year the consumption of calcium arsenate for boll-weevil control was decreased to about 26 million pounds largely due to its displacement by DDT.

A number of other arsenates including aluminium, magnesium, copper, lead and iron have been studied as insecticides. Arsenites likewise received some attention but most are too injurious to plants. Antimony is an element that is closely related to arsenic; it has been used in the form of tartar emetic (potassium antimony tartrate) for combating certain species of thrips.

Fluorine compounds

Inorganic fluorine compounds have been employed as insecticides for a long time; sodium fluoride (NaF) was probably the first (as a roach powder). In 1896 a British patent covering several fluorides, fluosilicates and borofluosilicates was issued. Sodium fluosilicate (Na_2SiF_6) at one time was widely used as a mothproofing agent. Cryolite or sodium fluoaluminate (Na_3AlF_6) finds limited use as an agricultural insecticide. Since about 1907 commercial mixtures of sodium fluoride and dinitrophenol known as Wolman salts have been used as wood preservatives, especially in Europe. Zinc fluoride has been used for the same purpose.

Sulphur

Elemental sulphur is a valuable insecticide and fungicide. It is the only pesticide in general use in the elemental form and in various compounds. As an insecticide, sulphur is used in dust form, as a wettable powder and as a diluent for other pesticides. From a historical standpoint, sulphur was probably the first chemical used for the control of plant-feeding mites. Sulphur is effective against a number of insects, especially scale insects on citrus fruit. With the advent of the newer organic insecticides its use has declined, but it is still valuable as a diluent or carrier and in combination with other chemicals. A lime-sulphur solution has been used in orchard practice since 1880. Its use as a sheep dip for the control of the scab mite is even older. About 1917 a dry lime-sulphur was developed to avoid handling the liquid concentrate. For the most part the dry lime-sulphurs are somewhat less effective than the solutions. Although still widely used as a spray material, the lime-sulphur solution has been supplanted in part by sulphur dusts, petroleum oil sprays, newer types of copper sprays and certain synthetic organic compounds.

Mercury compounds

Mercuric chloride (corrosive sublimate) and mercurous chloride (calomel) are the mercury compounds of most value in insect control. They have been used against fungus gnats, cabbage worms and onion maggots. Mercury compounds find their principal value as fungicides and are described below.

Fumigants

Fumigants are chemicals which in the gaseous state are toxic to insects. They are generally applied to plants or products in tightly enclosed spaces such as greenhouses, trees under tents, ships and closed grain warehouses. Fumigants are used to combat all kinds of insects. The vapours of burning sulphur were among the first fumigants used by man. Until the early 1920's hydrogen cyanide and carbon disulphide, which was used as early as 1854, were the most important commercial fumigants. Hydrogen cyanide was originally developed for the control of scale insects on citrus fruit. Carbon disulphide found wide use as a grain fumigant. Although efficacious, it is flammable and its vapours when mixed with air are highly explosive. This experience led to the search for less explosive fumigants. The application of synthetic organic chemistry has produced a large number of insect fumigants. Among those that have been widely used are methyl bromide, ethylene dibromide, ethylene oxide, chloropicrin, carbon tetrachloride, dichloropropane-dichloropropene (D-D), naphthalene and para-dichlorobenzene.

Fumigants are widely used against soil-infesting insects, nematodes, fungi and weeds. For this purpose, a gaseous or liquid fumigant is introduced into the loosened soil through furrows or drills with the expectation that it will distribute itself throughout an adjacent area.

Soil fumigation is growing in popularity, especially for treating seed beds. Carbon disulphide is one of the most efficient chemicals for soil treatment because of its vapour tension and penetrating qualities. D-D finds wide use as a soil fumigant in the control of various soil organisms including nematodes and insect larvae.

Oils

Petroleum oils

Marco Polo wrote at the end of the thirteenth century that crude mineral oil was employed for treating camels for mange. It was not until the second half of the nineteenth century, however, that systematic studies were undertaken to determine its value in insect control. On horticultural crops, oils serve as dormant sprays against scale insects, mites, insect eggs and certain hibernating caterpillars. They are used as additives to increase the effectiveness of other insecticides and as carriers for many insecticidal chemicals. In 1865, kerosene was recommended for the control of scale insects on orange trees. Because undiluted kerosene severely injured foliage and fruit, emulsions of oil in water produced at first merely by violent mechanical agitation and later with the aid of an emulsifying agent were substituted. Kerosene was gradually replaced by crude oils and eventually by highly-refined lubricating oils. For use as an insecticide, petroleum oils must meet certain specifications depending upon the purpose for which the oil is intended. Data commonly required are the viscosity, boiling range (for the lighter oils), density and sulphonation test. The latter indicates the percentage of the oil that does not react with sulphuric acid and is a measure of safety for application to plant and animal life. Dormant spray oils have a sulphonation test of 70—85 per cent and summer foliage oils of 90 to 98 per cent.

The use of petroleum oil in mosquito control has been a common practice for many years. Its use as a mosquito larvicide depends upon the distribution of a very thin film of oil over the surface of water inhabited by the larvae. The ideal oil must be toxic to the mosquito but largely non-toxic to plants, wildlife and humans. Although oil solutions containing DDT and other insecticides have reduced the consumption of petroleum oil for mosquito control, it is estimated that more than 1 million gallons of oil are still used annually in mosquito-control programmes.

Vegetable oils

Uncombined vegetable oils find little insecticidal application in the United States or in other countries with a highly developed petroleum industry. Olive, groundnut and palm oils have been recommended for spray emulsion purposes in Spain and northern Africa. Groundnut oil is used in France and elsewhere in Europe. Cottonseed oil is sometimes used in the Far East against cotton aphids, and rapeseed oil has been recommended in England because it is easily emulsified and has some value as an insecticide.

Plant materials

Plant materials are a source of some of the most useful insecticides. Tobacco, pyrethrum, derris, lonchocarpus, hellebore, sabadilla and quassia are some of the more important plants that were in use for many years prior to a systematic search for effective materials in the plant kingdom. The components of plant insecticides vary widely in their chemical composition. Tobacco, hellebore and sabadilla depend for their activity upon the alkaloids they contain. Alkaloids may be defined as nitrogenous bases and usually occur in plants as salts of acids, such as tannic, malic and citric. The insecticidal value of pyrethrum is due to its esters; the two principal esters are pyrethrins. Rotenone is the principal insecticidal constituent of derris and lonchocarpus. The nature of the insecticidal principle of quassia is unknown. All of the active insecticidal principles of plant insecticides possess complicated chemical structural formulae, and a comparison among them reveals no common grouping to which their activity might be attributed.

Nicotine

Insecticidal preparations made from the tobacco plant have been used for nearly two centuries. Both water extracts and the powdered leaves were used and exhibited high toxicity to soft-bodied insects, such as aphids. In 1828 the active pesticidal principle of tobacco was shown to be an alkaloid identified as 1-methyl-2-(3'-pyridyl) pyrrolidine. Nicotine alkaloid, nicotine sulphate and various fixed nicotines (e.g. nicotine bentonite) have been used as contact insecticides, fumigants and contact poisons. Many compounds that are derivatives of either pyridine or pyrrolidine have been synthesized and tested for their insecticidal properties, but only neonicotine was found to be of value as an insecticide. Subsequently an insecticidal alkaloid was found in the weed *Anabasis aphylla* and designated as anabasine. Chemical studies showed it to be identical with neonicotine.

Pyrethrum

The date of the first use of the pyrethrum plant, which is a species of chrysanthemum, as an insecticide is unknown. The daisy-like flower was probably first used in Iran. Its value was discovered in Dalmatia on the eastern shore of the Adriatic Sea about 1840. Dalmatia and adjacent areas were the most important growers and exporters of pyrethrum until the First World War when Japan became the leading producer. The industry began to flourish in Kenya about 1932, and by 1940 Kenya was the principal source. There is currently commercial production of pyrethrum in Brazil, Ecuador, Kenya and Zaire. The insecticide is found in the flower blossoms and is at a maximum in the fully opened blossom. Practically no insecticide occurs in the leaves and stems. Harvesting is manual as no practical mechanical harvester has been developed. Kenyan flowers contain about 1.3 per cent pyrethrins, Japanese and South American flowers about 0.9 per cent and Dalmatian flowers 0.7 per cent. About 1916, kerosene extracts of pyrethrum flowers were extensively used as a spray especially against houseflies and mosquitoes. Previously, only the finely ground blossoms had been used. The insecticidal principle of pyrethrum is unique in the rapidity with which the treated insects are paralysed. None of the other plant insecticides or the synthetic organic insecticides possess this rapid "knockdown" action.

The pyrethrins at one time were thought to be two esters known as pyrethrin I and pyrethrin II. Subsequent studies identified the presence of two additional insecticidally active esters. These have been designated as cinerin I and cinerin II.

Structural formulae for the pyrethrins were proposed about 1922 but it was not until 1938 that detailed structures of the pyrethrins and cinerins were determined with certainty. Structural studies were soon followed by attempts to synthesize the pyrethrins or closely related compounds designated as pyrethroids. One of these is allethrin, which is produced in sizable commercial quantities and is extensively used in fly sprays and aerosol bombs, but it has proved somewhat less effective than the natural pyrethrins as a general-purpose insecticide. The pyrethrins are used as household insecticides, grain protectants and insecticides against certain agricultural pests.

Rotenone and rotenoids

Although plants containing these products have been used as fish poisons for centuries, their application to combating many injurious agricultural insects only started about 100 years ago. Rotenone and the rotenoids are most frequently found in derris, lonchocarpus, tephrosia and mundulea; they are all members of the *Leguminosae* plant family. The roots of these plants are used either as finely ground dusts or as extracts made with organic solvents which remove both the rotenone and the rotenoids that are the principal insecticidal ingredients. Derris is a native of the Orient while lonchocarpus flourishes in the American tropics. In Peru, lonchocarpus is called cube or barbasco; in Brazil it is known as timbo. For many years, British Malaya and the Dutch East Indies were the principal sources of derris. Today most of the rotenone-containing material is imported into the United States from Peru as cube. The rotenone insecticides are of special value for the control of plant pests (especially where toxic residues are not desired) and cattle grubs.

The search for insecticides which might be used as substitutes for the more toxic arsenicals led to research in the late 1920's into the chemistry of derris extractives by workers in Germany, Japan, the United Kingdom and the United States. Rotenone, which is readily obtained in crystalline form from the roots of the plants, was shown to have the empirical formula $C_{23}H_{22}O_6$, and in 1932 the structure of the molecule was definitely established. Chemically, it possesses a rather complicated structural formula. It has three characteristic systems; a central dihydro-gamma-pyrone flanked on one side by a dihydro-benzopyran and on the other by a dihydro-benzofuran system. Numerous derivatives of rotenone and synthetic compounds related to parts of the molecule have been tested for insecticidal properties but without success. As with the other plant insecticides, derris and lonchocarpus have felt the inroads of the newer synthetic organic insecticides.

Synthetic organic compounds

From the standpoint of the chemist, insecticides may be divided into two broad classes; viz, inorganic and organic insecticides. Inorganic insecticides, such as those containing arsenic, lead or fluorine, owe their insecticidal properties primarily to those elements. Organic insecticides are compounds of carbon in combination with one or more elements such as hydrogen, oxygen, nitrogen, phosphorus, chlorine and sulphur. (Examples of synthetic organic insecticides are methyl bromide, paradichlorobenzene, DDT, benzene hexachloride and parathion.) Unlike the inorganic insecticides, the organic insecticides do not possess a specific element to which insecticidal properties may be ascribed. Their insecticidal action is due to a definite arrangement of the elements within the molecule and to the molecule as a whole rather than to a specific element or combination of elements. Many examples could be cited to illustrate this fact. For instance, there are three dichlorobenzenes having the formula $C_6H_4Cl_2$, but only paradichlorobenzene finds use as an insecticide. A more complicated case is benzene hexachloride. There are eight theoretically possible isomeric benzene hexachlorides having the formula $C_6H_6Cl_6$. Of the five isomers that have been prepared, only the gamma isomer (lindane) has outstanding insecticidal properties. Many other examples could be cited. Another characteristic of organic insecticides is that relatively minor modifications of their structures frequently lessen their insecticidal value.

Perhaps the first commercial use of an organic insecticide was in 1892 when the potassium salt of dinitro-ortho-cresol was marketed in Germany. It has had considerable usefulness as an insecticide (acaricide), as a dormant spray for aphids, mites and scale insects and as a toxic barrier against chinch bugs, grasshoppers and swarms of migratory locusts. In 1932 several organic thiocyanates were marketed on a sizeable scale in the United States for use as fly and cattle sprays and as household insecticides. The discovery of the insecticidal properties of DDT, however, is the most significant development in the field of insecticides in recent years.

Organic chlorine compounds

Dichlorodiphenyl trichloroethane (DDT). The insecticidal properties of DDT were discovered by Müller in Switzerland in 1939. When first used it possessed a remarkable degree of effectiveness against a large number of insects. It was the first synthetic insecticide to supplant the arsenicals for the control of such chewing insects as the codling moth on apples, the gypsy moth and spruce budworm on forest trees and the pink boll-weevil on cotton. Its prolonged stability to the action of light and air results in a residual deposit that kills untreated insects which crawl over them. DDT is also highly effective for the control of many insects of importance to public health. It was widely used during the Second World War for the control of typhus and as a larvacide for the control of the mosquito vectors of malaria, and it is still the most widely used insecticide for this purpose.

The development of resistance of the housefly as well as a number of agricultural insects has lessened the use of DDT in many areas. Its affinity for lipids resulting in storage in animal fats has further curtailed the use of DDT. There is no evidence of injury from these minute residues to man or his animals, however, and it is regarded by some toxicologists as a safe insecticide. It is ineffective against red spiders and other spider mites, the cotton boll-weevil and many aphids.

The insecticide DDT, which has the empirical formula $C_{14}H_9Cl_5$, contains 50 per cent chlorine. It is easily produced from the following readily available and inexpensive raw material: chloral, chlorobenzene and sulphuric acid. The technical DDT is essentially a mixture of two isomeric compounds comprising 65 to 70 per cent of p,p'-DDT and 30 to 35 per cent of o,p'-DDT.

Methoxychlor and TDE are closely related to DDT in chemical structure and have found wide use as insecticides. Methoxychlor, unlike DDT, is not stored in the fat of animals, but it is not as long lasting and it costs considerably more than DDT.

Benzene hexachloride. The outstanding insecticidal property of benzene hexachloride (BHC), also called hexachlorocyclohexane (HCH), was discovered independently and simultaneously in France and the United Kingdom during the Second World War when communication between the two countries was not possible. Theoretically, there are eight possible isomeric benzene hexachlorides, but only the gamma isomer (lindane) has insecticidal value. The name benzene hexachloride has been confused at times with hexachlorobenzene which is insecticidally inert but is valuable as a fungicide. Both products are obtained from benzene and chlorine. Benzene hexachloride is an addition product of benzene and chlorine and has the formula $C_6H_6Cl_6$, while hexachlorobenzene is a substituted benzene and has the formula C_6Cl_6. As benzene hexachloride is easily prepared from benzene and chlorine, both of which normally are readily available and low in cost, extensive commercial production of it was undertaken in Europe and the United States shortly after the end of the Second World War. The gamma isomer of the early commercial production ranged from 10 to 15 per cent, although there were occasional claims of 35 per cent. The impurified commercial product possesses a disagreeable pungent odour. Attempts at odour removal by treating solutions of the crude product in organic solvents with deodorizing absorbent materials met with erratic success. The gamma isomer of 97 per cent or higher purity has become an important insecticide under the generic name lindane.

Benzene hexachloride has exceptional value in the control of grasshoppers (locusts), cotton boll-weevils, wireworms and other soil pests. Lindane is used for poultry and livestock pests, seed treatment and for some agricultural crops. The use of benzene hexachloride on edible produce, however, has been severely hampered by the production of off-flavour. In the United States the use of benzene hexachloride on cotton grown in rotation with peanuts (ground nuts) has been discontinued because of off-flavour problems.

Cyclodienes. This group of insecticides comprises chlordane, heptachlor, aldrin, dieldrin, isodrin, endrin, endosulfan and toxaphene. All are highly chlorinated, cyclic hydrocarbons with characteristic "endo-methylene bridged" structures. With the exception of toxaphene, they are produced by a reaction developed by the German chemists Diels and Alder. Their discovery and development as insecticides are largely the result of the work of Hyman and his associates from about 1945. These insecticides are extensively used for the control of locusts, cotton boll-weevils and household insects, as soil insecticides and for many other purposes.

Chlordane made its commercial appearance as an insecticide soon after the end of the Second World War. Although the technical product contains a number of related compounds, the principal component comprises 60 to 75 per cent of octachloro-4,7-methanotetrahydroindane. Chlordane is obtained by the reaction of hexachlorocyclopentadiene and cyclopentadiene and treatment of the resulting compound with chlorine. Technical chlordane contains 64 to 66 per cent chlorine. It is a dark, viscous liquid, soluble in organic solvents and insoluble in water. Chlordane is effective against a wide variety of agricultural insect pests and certain cockroaches. It is used for the control of lice on cattle, hogs and horses.

Toxaphene was first tested against insects about 1945. It is prepared by the chlorination of the bi-cyclic terpene, camphene, to a content of 67 to 69 per cent chlorine and has the approximate empirical formula $C_{10}H_{10}Cl_8$. Toxaphene is a mixture of isomeric compounds, the exact structural formulae of which are not known. The technical product is a pale yellow, waxy solid soluble in the common organic solvents. Toxaphene is effective against a wide range of insects and is especially useful for the control of locusts, cotton boll-weevils and pests of livestock.

Strobane is similar in composition. It is obtained by the chlorination of camphene and pinene and contains 66 per cent chlorine. The insecticidal properties of strobane are essentially the same as those of toxaphene.

The highly chlorinated insecticidal compounds aldrin and dieldrin were introduced in 1948 by Hyman. Aldrin is produced by the Diels-Alder reaction of cyclopentadiene and acetylene and subsequent treatment of the reaction product with hexachlorocyclopentadiene. Chemically it is a hexachloro-hexahydro-dimethanonaphthalene. The pure compound is a white crystalline compound; the technical product is a brown, waxy solid with 90 per cent content of the principal insecticidal ingredient. Aldrin is effective against a wide range of insects and finds extensive use for soil treatment. In the soil as well as in plants and animals, aldrin is converted by oxidation into its epoxide, dieldrin; its insecticidal properties are similar to those of aldrin.

Isodrin is an isomer of aldrin; that is, it has the same empirical formula as aldrin but differs in its spatial configuration. Endrin is an epoxide of isodrin. It has the same relation to isodrin as dieldrin does to aldrin.

Organic phosphorus compounds

This class of compounds was discovered in the late 1930's by Schrader in Germany, but their outstanding insecticidal value did not become generally known until about 1945. Tetraethyl pyrophosphate was the first to become commercially available in the United States. It is highly effective and rapid in its action on aphids, spider mites, small caterpillars and many other insects. It is highly toxic to man and other animals. In water solution it soon decomposes by hydrolysis into non-toxic water-soluble products. Tetraethyl pyrophosphate was soon followed by parathion. It exerts a rapid kill of a wide variety of insects and is highly toxic to man. It is comparatively stable and the spray or dust residue remains effective for several days. The discovery of the outstanding insecticidal properties of tetraethyl pyrophosphate, parathion, octamethyl pyrophosphoramide and others stimulated research in this field, and hundreds of organic phosphorus compounds of many types have been evaluated for insecticidal properties. Among those commercially available are demeton, EPN, trichlorfon, malathion, diazinon, ronnel and dioxathion. Millions of pounds of parathion have been used annually but its use may be curtailed by the introduction of less hazardous compounds, such as malathion, chlorthion and diazinon.

Carbamates

These insecticides were introduced in the field of pest control about 1952 by the Geigy Company, Switzerland. The early compounds were carbamic acid esters of heterocyclic enols. The carbamates are potent systemic insecticides which are highly selective in their action. Dimetan and isolan have a rapid pyrethrum-like action on flies and have been used commercially as contact insecticides against aphids, thrips, granary weevils and other small insects. Intensified research by several companies on carbamate insecticides revealed several compounds having potent broad-spectrum insecticidal properties. Of these, carbaryl (marketed under the trade-name Sevin) has achieved widespread use as a broad-spectrum insecticide effective against many insect pests of fruits, vegetables, cotton and other crops. Carbaryl, however, is relatively ineffective against aphids and spider mites.

HERBICIDES (WEED KILLERS)

Though chemicals have been used for many years to control weeds, no large-scale applications were made before 1930. Up to 1942, the chemicals in use were contact herbicides and soil sterilants, such as arsenicals, chlorinates, benzenes, chlorates, sulphuric acid, sulphates, substituted phenols and oils. Sodium arsenite was widely employed for weed control along railroad tracks, and diesel oil was used along highways. The discovery of the herbicidal action of 2,4-dichlorophenoxyacetic acid (2,4-D) in 1944 had far-reaching effects on weed control. Within five years after its discovery and the demonstration of its selective action, 2,4-D was used to control weeds on more than 18 million acres of small grain and 4.5 million acres of maize in the United States. This spectacular use stimulated the chemical industry in Europe and the United States to synthesize and evaluate the weed-killing properties of hundreds of chemicals. As a result, about 135 effective and selective organic herbicides are today available to farmers and home owners. The chemical formulae of herbicides cover the wide range of phenoxy compounds, aliphatic acids, phenols, benzoic acids, carbamates, substituted ureas, triazines and others. The use of herbicides in the United States more than doubled between 1959 and 1963; an estimated 85 million acres or about 20 per cent of the cropland was treated in 1962.

Oils have gained commercial use as weed killers since about 1940. Most are by-products of petroleum distillation. They act as contact herbicides and may be selective or general as weed killers. Diesel oils which are usually moderately heavy low-grade oils are generally too toxic to plants for selective weed control. In addition to treating cropland, herbicides are used to control weeds that clog irrigation and drainage canals and interfere with the use of ponds, lakes and streams.

In view of the susceptibility of many vegetable crops to injury by herbicidal sprays, treatments may be made prior to emergence of a specific crop or weed. Such treatment is spoken of as pre-emergence treatment. Post-emergence treatment is any treatment after emergence of a specified crop or weed. For example, 2,4-D gives effective post-emergence control for most broadleaf weeds in maize, sorghum grains and grass pastures.

FUNGICIDES

Fungicides are used to control plant diseases on many crops. The fungicides are applied to the seed to prevent rotting or to foliage as sprays or dusts to protect the plant by destroying the spores of the fungi before they penetrate the foliage and cause infection. Every crop plant is prone to one or more plant diseases, such as blight, smut, scab, wilt, mildew and rust caused by fungi, bacteria and viruses. No effective chemical is available for bacterial diseases or viruses although the antibiotic streptomycin has been used with some success against fireblight on apples and pears.

Copper, sulphur and mercury compounds were relied upon from earliest times as fungicides. Over 3,000 years ago, sulphur was recognized for its fungicidal and insecticidal properties. Mercuric chloride was recommended as a wood preservative in the eighteenth century. In 1882, Millardet of Bordeaux, France, discovered that a mixture of lime and copper sulphate is effective in protecting grape foliage from downy mildew. This mixture became known as Bordeaux mixture and was used for many years as a fungicide. On certain plants Bordeaux mixture produced injury. In 1905, lime-sulphur, which is a mixture of calcium polysulphide formed by boiling sulphur and lime in water, was introduced. It was exceptionally efficient against apple scab and eliminated the russeting of fruit that followed the use of Bordeaux mixture. From 1907 until about 1930, both Bordeaux mixture and lime-sulphur were used extensively to prevent fungus diseases on fruits and vegetables. In 1934, the dithiocarbamates were patented as fungicides but were not marketed for almost ten years. In 1940 chloranil (tetrachlorobenzoquinone) was introduced as a practical seed protectant. An outstanding authority on fungicides, Robert Horsfall, believes that chloranil triggered the use of organic compounds in agriculture. Previously these fungicides had been regarded to be too expensive for farmers. Today the following organic fungicides are available for use on fruits and vegetables: nitropyrazole, quinoline, phenol, glyozalidine, iron, copper and manganese salts of dimethyldithiocarbamic acid and captan.

In this brief summary of the history of pesticides, insecticides may appear to have been presented in greater detail than the other pesticides. This is due in large part because of their longer history, and the fact that the number of injurious insects far exceeds the number of all the other pests combined. It does not mean, however, that fungicides, herbicides or nematicides are less important. It may well be that the potential in future chemical control of these pests is far greater than the future of insecticide use.

4. THE EVOLUTION OF PESTICIDE ANALYSES*

*by Gunter Zweig***

In the good old days before the 1940s, farmers around the world sprayed their crops with well-tested insecticides such as lead, arsenic, fluoride and possibly exotic natural extracts like nicotine, pyrethrin and rotenone. Those were the days when the Food and Drug Administration (FDA) only occasionally inspected and analysed fruits, vegetables or dairy products for residual pesticides. Housewives reminded their children to wash the fruit before eating, thus probably removing surface residues of the inorganic pesticides. It was common then that a "worm" (larva of the codling moth) might crawl out of the apple, and that rotten spots had to be eviscerated from raw fruits and vegetables.

However even in those good old days, the California State Government in 1927 instituted a law[1] regulating the permissible residue for Paris green and later for lead, arsenic and fluoride in raw agricultural crops at 3.5 to 7.0 ppm (milligram per kilo of fresh weight). Quantitative analytical methods devised by Hoskins and Ferris[2] and by Cassil and Wichmann[3] were used by government inspectors to enforce the pesticide laws.

However, the peaceful days of pesticide usage were soon to be shattered. While screening insecticides in 1939, the Swiss organic chemist Müller came across a chlorinated biphenyl compound, 4,4'-dichlorodiphenyl trichloroethane (DDT) which had actually been synthesized in the nineteenth century by Zeidler.[4] During the Second World War, German chemists discovered a new class of powerful insecticides, the organophosphates.[5] At the same time, American and British research workers came across a completely new class of compounds, the

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[1] *California Agricultural Code, Division 7, Agricultural Chemicals, Livestock Remedies, and Commercial Feeds* (1927) chapter 1.

[2] Hoskins, W. M. and C. A. Ferris (1936) *Industrial and Engineering Chemistry, Analytical Edition*, Vol. 8, p. 6.

[3] Cassil, C. C. and H. J. Wichmann (1939) *Journal of the Association of Official Agricultural Chemists*, Vol. 22, p. 436.

[4] Zeidler, O. (1874) *Berichte*, Vol. 7, p. 1180.

[5] Schrader, G. (1963) *Die Entwicklung neuer insektizider Phosphorsaure-Ester*, 3rd ed., Verlag Chemie, Weinheim/Bergstr.

synthetic plant hormones of the phenoxyalkyl acid type with its best known representative 2,4-D (2,4-dichlorophenoxyacetic acid).[6] Thus, during the middle 40s, an agricultural revolution of synthetic organic insecticides and herbicides took place; 25 years later it shows no abatement. The production and use of these chemicals during the past two and one-half decades have grown to approximately 500 million kg valued at $750 million in the United States alone.[7]

The United States Government took the initiative and enacted regulations which would accommodate the synthetic pesticides under existing food and drug legislation. Public Law 518 (the Miller Bill) was an amendment to the Federal Food, Drug, and Cosmetic Act of 1938. The concept of the amended law pertaining to pesticides was that the presence of any poisonous or deleterious pesticide chemical in the daily diet of the population was undesirable unless a "safe" tolerance for these chemicals had been established by the government. Safety was based on factors such as the smallest quantity that induced physiological changes in experimental animals, a built-in safety factor of 100, the percentage of a certain food in the daily diet of the population and the possible induction of cancer in man or animal. This last restriction, known as the Delaney Clause of 1958, made it mandatory for the establishment of a zero tolerance of any cancer-inducing pesticide chemical.

THE CONCEPT OF TOLERANCE

The zero tolerance

As already mentioned, the legislators introduced the concept of a zero tolerance for certain pesticides used in agricultural crops without much concern about chemical reality. Furthermore, analytical chemists could not accept in good conscience the concept of "no residue" used by the United States Department of Agriculture (USDA) in the registration of pesticide chemicals which under good agricultural practices could be shown not to leave "any residue" on the raw agricultural crop (see chapter 2).

An additional complication was that the Secretary of Health, Education and Welfare could invoke a "zero" tolerance for certain foods such as milk, on the advice of a knowledgeable group of scientists. This indeed was the case for methoxychlor, a pesticide related in structure to DDT, for which the E. I. Du Pont de Nemours Company requested a 0.25 ppm tolerance in milk. A scientific advisory committee recommended that the petition by the manufacturer be denied. The zero tolerance for any pesticide chemical in milk and milk products (such as ice cream and butter) became the accepted regulation. However, a tolerance for DDT in the fat of beef cattle was established and found to be acceptable. The situation was complex and unrealistic. Strict enforcement would have eliminated the use of many pesticides on the farm.

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[6] Zimmerman, P. W. and A. E. Hitchcock (1942) *Contributions of the Boyce Thompson Institute*, Vol. 12, p. 312.

[7] United States Tariff Commission (1968) *Synthetic Organic Chemicals, U.S. Production and Sales of Pesticides and Related Products*, Washington, D.C.

Three incidents took place during the past decade that disturbed the scientific community and resulted in modifications of the zero tolerance. The first incident took place in Oregon and Massachusetts one week before Thanksgiving in 1959, when the FDA confiscated most of the cranberry harvest for that year and even tins of berries from harvests of previous years. The reason for the seizure was that small traces of amino-triazole herbicide had been detected by FDA chemists. A zero tolerance for amino-triazole had been established previously based on the observation of a cancer or tumour in experimental rats during acute-feeding studies. The method of analysis which had been used to detect finite quantities of amino-triazole was ion-exchange purification followed by the production of a colour and spectrophotometric determination of the absorbency. This period in time is referred to by some pesticide chemists as B.C. and A.C. (before and after cranberries). It marked a critical turning point for the analyses of the proverbial zero molecule. Once a zero tolerance based on a certain analytical method had been established and its inherent sensitivity and specificity were known, a new, alternate procedure developed later might be used to detect zero molecules, which, if enforced, would result in seizures of food and crops by government inspectors.

The second incident was the problem of contaminated dairy products. On 28 January 1960, Hawaiian newspapers reported that United States Government health authorities had seized about 920 pounds of butter contaminated with insecticides. The butter had been shipped from the mainland but none of it had been sold. The impracticality of the zero tolerance in milk for pesticides was clearly demonstrated by the analysis of paper chromatography of chlorinated pesticides using methods perfected by Mills[8] and Mitchell.[9] A large number of milk and butter samples which were examined contained finite, detectable quantities of chlorinated pesticide residues probably as the result of the presence of these pesticides in the feed of dairy cattle. Zweig and associates[10] showed that 0.5 ppm of DDT in the feed of dairy cattle resulted in no detectable residues in the milk on the basis of the colorimetric procedure of Schechter and Haller.[11] However, 1 ppm of DDT in the feed resulted in detectable residues of this insecticide in the milk. These studies have been verified by Archer using gas-liquid chromatography with a much greater sensitivity than the colorimetric procedure.[12] The revelation that pesticide residues were found in a great number of milk and butter samples, even though present in quantities less than 0.1 ppm, nevertheless, caused a dilemma for the government. Milk and butter samples containing more than one molecule of pesticides should have been subject to

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[8] Mills, P. A. (1959) *Journal of the Association of Official Agricultural Chemists*, Vol. 42, p. 734.

[9] Mitchell, L. C. (1958) *Journal of the Association of Official Agricultural Chemists*, Vol. 41, p. 781.

[10] Zweig, G., L. M. Smith, S. A. Peoples and R. J. Cox (1961) *Journal of Agricultural and Food Chemistry*, Vol. 9, p. 481.

[11] Schechter, M. S., S. B. Soloway, R. A. Hayes and H. L. Haller (1945) *Industrial and Engineering Chemistry, Analytical Edition*, Vol. 17, p. 704.

[12] Crosby, D. G. and T. E. Archer (1966) *Bulletin of Environmental Contamination and Toxicology*, Vol. 1, p. 16.

seizure. To illustrate the impracticability of such a narrow view is to consider that one litre of milk containing 10^{-9} g of DDT (the smallest quantity detectable by modern analytical techniques) would still contain 2×10^{12} molecules of the pesticide.[13]

By late 1968, the Federal Government had relaxed its view on the zero tolerance and no-residue concepts. Both terms have been eliminated in the vocabulary of government regulations and the terms "inconsequential" or "insignificant" residues have been adopted. This means that chemically finite tolerances can now be established which are based on the stated method of analysis. This does not preclude, however, the right of the Government to lower the finite residue or tolerance if more sensitive analytical techniques or new toxicological data are developed at a future date. Finite tolerances for insecticides in dairy products have now been granted and will be established for all previous no-residue registrations.

The third incident which truly revolutionized the entire concept of "safe" pesticide residues and tolerances was the publication of Carson's[14] *Silent Spring* in 1962. It became a best seller immediately and had an explosive effect on the general public by revealing that foodstuffs "had been contaminated" by poisonous pesticide chemicals. The pesticide community, including personnel at university experimental stations, agricultural chemical companies, toxicology departments and governmental agencies, had long known about safe levels of pesticides and the presence of low residues in the daily diet. However, it has always been difficult to explain to the public that the presence of minute quantities (more than one molecule) of a poisonous chemical may be inconsequential to public health. It is admitted that the pesticide community was amiss by not informing the public. This is why Carson's revelation made such an impact on the average citizen. The beneficial results of Carson's book were the expenditure of greatly increased governmental funds for studies of the analytical technology of pesticides, toxicology and the ecological effects of pesticides. Furthermore, Carson's book has resulted in the decreasing use of non-biodegradable pesticides. The search for safer and less persistent pesticides by chemical companies and the search for alternate methods of pest control like biological control, irradiation and third-generation pesticides (juvenile hormones).[15]

The search for zero

One of the culprits of the pesticide revolution started by the first synthetic organic pesticide was the pesticide residue chemist. For years he has striven to devise more sensitive and specific methods of analysis and has enriched the chemical vocabulary with terms like microgram (10^{-6} g), nanogram (10^{-9} g) and picogram (10^{-12} g). (See table 1.) If it had not been for the refinement of analytical techniques, the illusions might still exist of zero residue or no residue in crops which have been sprayed with pesticides. Since no residues could be

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[13] Zweig, G. (1964) *Chromatographic Reviews*, Vol. 6, p. 110.
[14] Carson, R. (1962) *Silent Spring*, Houghton Miffin, Boston.
[15] Williams, C. M. (1967) *Scientific American*, Vol. 217, p. 13.

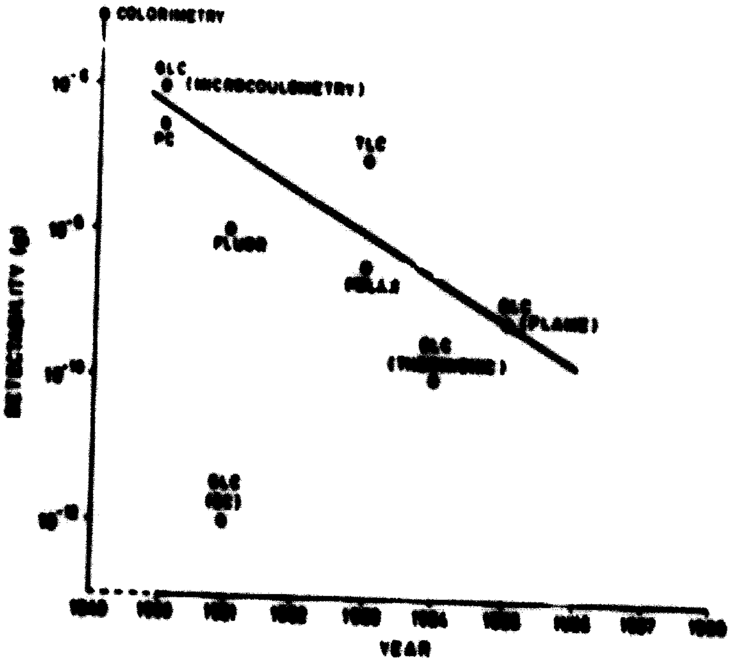
detected by conventional colorimetric methods, it seemed that the applied pesticide chemical had disappeared as if by magic. Perhaps some of the applied pesticide had disappeared by translocation in plants, volatilization, chemical or metabolic transformation and degradation. The specific colorimetric method did not always reveal clues about the biological transformation of the parent compound to potentially more toxic metabolites, as for example parathion to para-oxon, heptachlor to the epoxide and aldrin to dieldrin.

TABLE 1. CONVERSION TABLE OF WEIGHT UNITS USED IN RESIDUE ANALYSES OF PESTICIDES

(1 g = 10^3 mg = 10^6 µg = 10^9 ng = 10^{12} pg)

Unit		*gram*
picogram (pg)	=	10^{-12}
nanogram (ng)	=	10^{-9}
microgram (µg)	=	10^{-6}
milligram (mg)	=	10^{-3}

Figure 1. The progress of analytical methods of residue analysis from 1940 through 1968



Key: GLC — gas liquid chromatography; FLUOR — fluorometry; TLC — thin-layer chromatography; PC — paper chromatography; EC — electron-capture detection; colorimetry

Table 2 is a summary of approximate limits of detection of pesticides by various analytical techniques. In figure 1, the limits of detectability are plotted against the year in which the method became practical. It is seen that the analytical world has shrunk from about 25 μg to 0.1 pg during the past 25 years. In other words, the sensitivity for the detection of pesticides has been increased by a factor of 250 million!

TABLE 2. APPROXIMATE LIMIT OF PESTICIDE DETECTION

Method of analysis	*Pesticide*	*Detectability (g)*
Colorimetry	DDT, Parathion	10^{-5}
Fluorometry	Guthion	10^{-8}
Infra-red spectrophotometry	Endosulfan	10^{-5}
Oscillography	DDT	5×10^{-6}
Paper chromatography	Parathion	4×10^{-9}
Thin-layer chromatography	DDT	10^{-7} to 10^{-6}
Gas-liquid chromatography	Chlorinated and Phosphate	10^{-7} to 10^{-5}
Detector		
Katharometer	Endosulfan	2.5×10^{-5}
Electron-capture	DDT	10^{-12}
Microcoulometry	DDT	10^{-6}
Thermionic	Parathion	10^{-10}
Flame photometry (phosphorus mode)	Dimethoate	10^{-9}
Flame photometry (sulphur mode)	Omite	2×10^{-8}

Another way of demonstrating the great strides which have been made in increasing the sensitivity of residue analysis methods is shown in table 3. During the eight-year period from 1955—1963, the sensitivity for the detection of DDT in milk, for example, was increased from 0.1 ppm to 0.001 ppm.

TABLE 3. IMPROVED DETECTION LIMITS OF PESTICIDE RESIDUES IN AN EIGHT-YEAR PERIOD

Pesticide	*Crop*	*ppm*	
		1955	*1963*
Endrin	Cabbage	0.2	0.03
DDT	Maize	0.1	0.02
DDT	Butter and animal fat	2.5	0.01
Chlordane Heptachlor	Groundnuts	0.1	0.01
Dieldrin	Potatoes	0.1	0.01
Aldrin	Alfalfa	0.1	0.01
DDT	Milk	0.1	0.001

Source: Benvenue, A. (1967) *Analytical Methods for Pesticides, Plant Growth Regulators and Food Additives*, Vol. V, ed. by G. Zweig, Academic Press, New York, chapter 1, p. 5.

In the beginning of the pesticide era, 20 to 25 μg of arsenic could be detected by the Gutzeit method[16] or a modified, volumetric micromethod.[17] The Schech-

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[16] Gunther, F. A. and R. C. Blinn (1955) *Analysis of Insecticides and Acaricides*, Interscience Publishers, New York.

[17] Cassil, C. C. and H. J. Wichmann, *op. cit.*

ter-Haller colorimetric procedure for DDT and the Averell-Norris method[18] for parathion extended the range of sensitivity to about 2 μg. The advent of paper and thin-layer chromatography increased the detectability to 0.1 μg and added another parameter, namely the physical separation of mixtures of pesticides and metabolites. By the use of specific colour spray reagents, different pesticides and metabolites could be identified. By using an enzyme spray reagent containing cholinesterase, the biological activity of spots separated by chromatography[19] could be ascertained.

Gas-liquid chromatography with specific detectors for halides, sulphur, phosphorus and nitrogen has further enhanced the ease with which complex mixtures of pesticides can be quickly separated and identified. The specific organophosphate detector is capable of detecting as little as 0.04 ppm pesticide in water.[20] The electron-capture detector[21] is capable of producing a significant signal for 0.1 pg of lindane and 1 pg of DDT.

Attempts to link gas-liquid chromatography to rapid infra-red analysis or mass spectrometry are still in their infancy. However, as instrumentation is improved, these sophisticated and absolute methods of identification should achieve the sensitivity required for pesticide residues and be within practical reach of the residue chemist as was predicted by the author[22] in 1964.

CLEAN-UP PROCEDURES

The search for zero as discussed above may be misleading; by increasing the absolute sensitivity of the final method of analysis, the over-all detectability of pesticide residues in crops is not necessarily improved. The final extract must be sufficiently purified in order to minimize possible interferences in the last analytical step. These interferences may be caused by natural constituents in foods and crops such as oils, fats or pigments. The substances may cause tailing of chromatographic eluates, clogging of syringe needles and overloading of detectors, columns, papers or thin-layer plates. General clean-up methods are desirable and have been attempted along the following lines.

Chromatographic techniques using Florisil adsorbent (15 per cent MgO and 84 per cent SiO_2) have shown the greatest popularity. Three independent laboratories tested the standardized and commercially available absorbent Florisil PR and found excellent reproducibility for the elution of seven chlorinated pesticides in maize and spinach.[23] Nearly quantitative recoveries were achieved when the elution volumes were adequate.

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[18] Averell, P. R. and M. V. Norris (1948) *Analytical Chemistry*, Vol. 20, p. 753.

[19] Menn, J. J. and J. B. McBain (1966) *Nature*, Vol. 209, p. 1351.

[20] Zweig, G. and J. M. Devine (1969) *Residue Reviews*, Vol. 26, p. 17.

[21] Bonelli, E. J., H. Harrmann and K. P. Dimick (1964) *Journal of Agricultural and Food Chemistry*, Vol. 12, p. 333.

[22] Zweig, G., *op. cit.*

[23] Beckman, H. *et al.* (1967) *Journal of the Association of Official Analytical Chemists*, Vol. 50, p. 1251.

An attempt was made by the author[24] to devise a general clean-up method by utilizing a gas chromatography apparatus without detector that was supplied with a simple glass collector at the end of the column. The collector was fashioned from a length of tapered glass tubing packed with solvent-moistened glass wool. This technique proved effective for the residue analyses[25] of two isomers of endosulfan in a variety of crops by infra-red spectrophotometry as will be discussed in detail below. A similar approach has been suggested for the clean-up of samples prior to thin-layer chromatography.[26] The flaw in these methods, however, lies in the unpredictable chromatographic behaviour of pesticides in the presence of large amounts of interfering substances which may be causing retardation and asymmetry of effluent peaks. Since the work is performed without a detector signal, it is conceivable that low recoveries of pesticide residues may result.

Another novel approach to a general clean-up method has been the sweep co-distillation technique for pesticides in oily crops.[27] Figure 2 depicts the parts of the sweep co-distillation assembly.[28] The advantages of this method over the previously described gas-chromatographic clean-up are the effective removal of interfering substances by adsorption in the first vertical column and the co-distillation of solvent and pesticides at elevated temperatures (250° C) and fast nitrogen gas flow (600 ml/min). The vapours are condensed in the ice bath and over Anakrom and the solution is collected in the receiving tube in which it can be concentrated.

Since most crude plant extracts must undergo some measure of clean-up, it is recommended first to attempt acetonitrile partition followed by Florisil chromatography; if these techniques fail, sweep co-distillation should be attempted.

A simple calculation emphasizes the importance of distinguishing between the sensitivity of the final step in the analysis and the over-all sensitivity of the pesticide residue determination. The following factors may be considered: hypothetical sensitivity of detection of 1 ng, final volume of the extract of 1.0 ml, concentration factor of 10 (volume/weight) and the aliquot to be analysed of 0.01 ml. The calculated over-all sensitivity of the method is 0.01 ppm. In most cases this sensitivity is acceptable to prove the absence of a particular pesticide in order to satisfy the old zero tolerance. If the sensitivity of detection could be further increased to the picogram range which is certainly possible with electron capture detection (see table 2), the over-all sensitivity of the residue method may be improved to 0.00001 ppm or 0.01 parts per billion. Alternately, the

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[24] Zweig, G. and R. E. Breidenbach (1961) American Chemical Society Meeting, Chicago, Abstract 20 A.

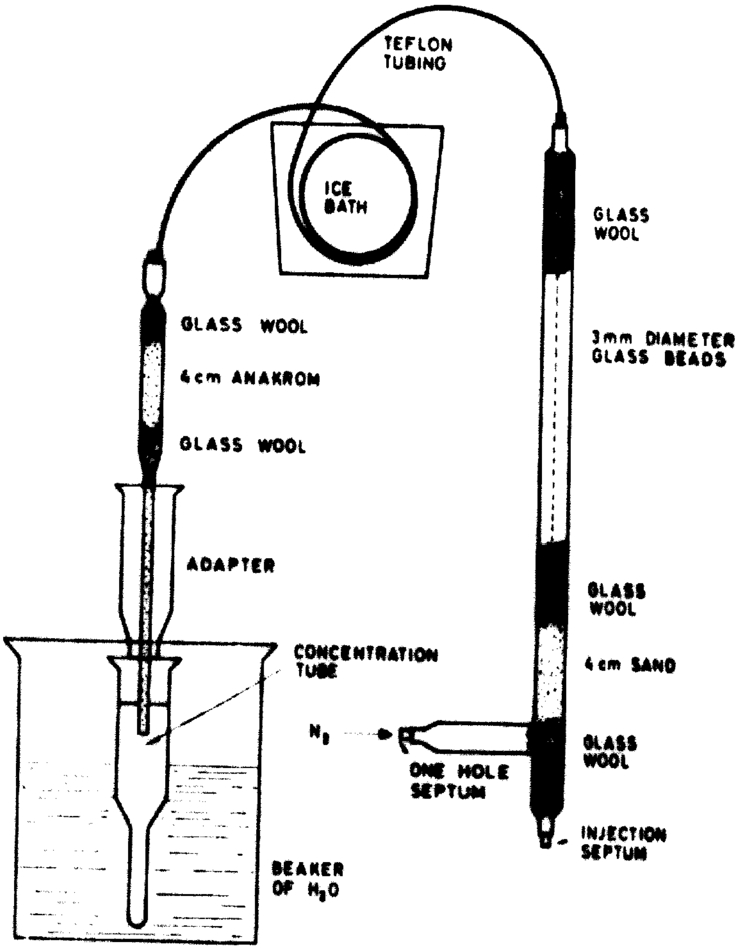
[25] Zweig, G., T. E. Archer and D. Rubenstein (1960) *Journal of Agricultural and Food Chemistry*, Vol. 8, p. 403.

[26] Hartman, K. T. (1967) *Journal of the Association of Official Analytical Chemists*, Vol. 50, p. 615.

[27] Storherr, R. W. and R. R. Watts (1965) *Journal of the Association of Official Agricultural Chemists*, Vol. 48, p. 1154.

[28] Storherr, R. W., E. J. Murray, I. Klein and L. A. Rosenberg (1967) *Journal of the Association of Official Analytical Chemists*, Vol. 50, p. 605.

Figure 2. The sweep co-distillation assembly for general clean-up of pesticides in oily crops



dilution factor may be omitted or the aliquot to be analysed decreased, thus simplifying the experimental procedure and minimizing interferences.

SPECTROPHOTOMETRIC METHODS

With the availability of commercial spectrophotometers scanning the ultra-violet, visible (colorimetric methods) and infra-red regions, specific methods for residue analyses of pesticides were developed. The Miller amendment of the food and drug laws made it mandatory that a company furnish a specific analytical method to be applicable for the purpose of enforcement before an official tolerance would be granted.

Limited by radiation intensity of the source and the sensitivity of detectors, most spectrophotometric methods are useful in the microgram range. Sensitivity can be increased by greater path lengths of cells for the ultra-violet and visible regions or by microbeam attachments for infra-red spectrophotometers. However, with increased sensitivity, often the interferences of extraneous substances are enhanced, or the noise-signal ratio may not be improved correspondingly.

Besides the limited sensitivity for spectrophotometric methods, another disadvantage ironically is the specificity of these methods, thus a multi-component mixture has to be analysed by multiple methods. Conversely, possible metabolites, like para-oxon (the oxygen analogue of parathion) cannot be distinguished by the colorimetric methods.[29] Some colorimetric analyses are extremely lengthy but are still useful for formulation analyses or for a large number of routine samples. Once the routine even for a rather lengthy procedure has been developed, a skilled laboratory technician can handle eight to ten analyses during a working day.

Colorimetric procedures

The necessary steps to develop a coloured derivative or to read directly the absorbency in the ultra-violet or infra-red region are given as illustrations of colorimetric procedures. The procedure for the colorimetric residue method for aldrin is as follows.[30]

After solvent extraction and chromatographic clean-up, the solution is reacted with phenyl azide reagent which must be prepared in the laboratory and purified daily by column chromatography. Excess reagent is removed by evaporation, and the resultant triazole is coupled with diazotized dinitroaniline. After acidification, the adsorbency is measured at 515 nm; appropriate crop blanks and standards ranging from 5 to 40 μ/ml are taken through the colour reaction steps and final readings corrected for interferences. One may compare this laborious method with the single-step gas-chromatographic technique (see below) by which a complete analysis requires less than 10 minutes at a sensitivity 1,000 times greater than that for the colorimetric method!

Probably the best known colorimetric method of analysis for a particular pesticide is the Schechter-Haller method[31] for DDT. The plant material to be analysed for traces of DDT is extracted with a suitable solvent and evaporated. The residue containing the suspected insecticide (DDT) is nitrated with fuming nitric acid; the resultant tetranitro compound is extracted into ether, washed with dilute base, taken to dryness and finally reacted with sodium methylate. The colour reagent should be prepared in the laboratory using anhydrous methanol, which must be processed. The resultant colour is measured with a spectrophotometer at 596 nm at a sensitivity of about 10 μg yielding an absorbency of about 0.1.

Although ten years have passed since the author and associates[32] have analysed milk samples for DDT by the above method, it might be of interest to calculate the approximate time period involved to analyse four milk samples for DDT including a calibration curve of four points in duplicate. The assumption is made that all reagents are ready for use. The following approximate times (in hours) have been calculated:

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[29] Averell, P. R. and M. V. Norris, *op. cit.*

[30] Porter, P. E. (1964) *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives, Vol. II Insecticides*, edited by G. Zweig, Academic Press, New York, pp. 1–24.

[31] Schechter, M. S. *et al.*, *op. cit.*

[32] Zweig, G. *et al.*, *op. cit.*

Evaporation of samples	2.0
Nitration	1.5
Extraction and washing	2.0
Evaporation	1.0
Colour development and reading	0.5
TOTAL	7.0

To the total time should be added at least another hour for dish-washing and 30 minutes for lunch. During one working day, four DDT samples can be efficiently analysed. As will be discussed below, chromatographic methods of analysis (paper, thin-layer and gas-liquid chromatography) are much less time-consuming, more sensitive, more accurate at low levels and suitable for multiple analyses of closely related pesticides.

Infra-red spectrophotometry

Although infra-red spectrophotometry is a highly useful tool for the qualitative and quantitative analyses of pesticide formulations,[33] its adaptation to residue analyses is greatly restricted by the relatively large quantities of pure material which must be isolated. The development of microbeam condensing units for solid KBr samples and long-path cells for solutions has increased the sensitivity to the microgram range. However, the noise-signal ratio of the instrument and interferences by solvents and plant constituents have not been favourable to increase the reliability of infra-red techniques at the submicrogram level.

Zweig *et al.*[34] detected 4 μg of endosulfan from pears and alfalfa after cleaning crude plant extracts by gas chromatography. Fractions were collected in solvent traps at pre-determined retention times under rigidly controlled conditions. The final solution was made in 0.2 ml of carbon disulphide in 3 mm path-length cells, and the unique peak of endosulfan at 8.37 μm was measured at a fivefold scale expansion of the instrument. A slight modification in the collection trap consisted of condensing the effluent gas stream directly on powdered KBr which was pelleted for micro-infra-red analysis.[35]

A similar procedure as that described above for endosulfan has been extended to the μg range of organophosphate insecticides in a variety of fruits and vegetables.[36] At levels below 20 μg, however, even qualitative identification became uncertain due to losses of insecticide at each stage during the procedure and the lack of sensitivity of infra-red detectors.

It was anticipated by the author in 1960 that the combination of gas chromatography and infra-red spectrophotometry would be widely accepted for pesticide residue analyses provided that the following equipment was developed:

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[33] Bruce, R. B. (1963) in *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives, Volume I*, edited by G. Zweig, Academic Press, New York, pp. 149–167.

[34] Zweig, G. *et al.*, *op. cit.*

[35] Giuffrida, L. (1965) *Journal of the Association of Official Agricultural Chemists*, Vol. 48, p. 355.

[36] Crosby, N. T. and E. Q. Laws (1964) *Analyst*, Vol. 89, p. 319.

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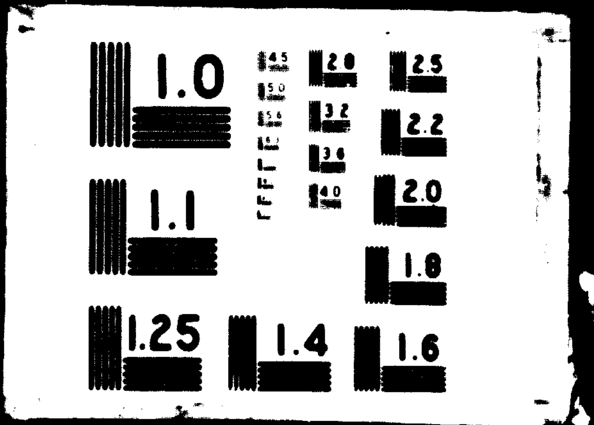

sensitive thermopile detectors, liquid flow-through cells and rapid-scanning infra-red spectrophotometers. Although rapid-scanning spectrophotometers have become available commercially, their sensitivity has not been extended into the submicrogram range. However, it seems that a quantum jump has taken place during the past ten years by combining gas chromatography with mass spectrometry rather than with infra-red for the qualitative analyses of trace amounts of organic compounds.

Fluorescence techniques

Fluorescence spectrophotometric techniques for trace analyses of pesticides appear to have the advantages of greatly increased sensitivity and specificity. The calculated ultimate sensitivity of fluorescence and colorimetry for three pesticides is compared in table 4. The pesticide Co-Ral, for example, can be detected at nanogram levels by the fluorescence technique. Specificity is imparted by characteristic excitation and fluorescence wavelengths. In order to measure emitted fluorescence, it may be necessary to modify the non-fluorescent parent compound by hydrolysis, oxidation or the formation of metal chelates.[37]

TABLE 4. ULTIMATE SENSITIVITY OF FLUORESCENCE AND COLORIMETRIC METHODS

Compound	*Colorimetry (μg)*	*Fluorometry (μg)*	*Calculated ratio*
	(1)	(2)	(1)/(2)
Co-Ral	2.5	0.002	1250
Guthion	1.6	0.01	160
DEF	10.0	0.02	500

Although spectrofluorometric techniques seem to be ideally suited for trace analyses of some pesticides, there are inherent difficulties. Most extracts from biological materials contain interfering, fluorescent substances which mask the characteristic fluorescence of the pesticides under investigation. In pesticide analyses, a rule of thumb is that the signal for the treated sample must be at least twice that of the background from the reagent or untreated samples. This requirement necessitates clean-up procedures in which the extraneous, unknown fluorescent materials can be separated from the fluorescent pesticide or conversion product. Examples of these separations are removal of interferences into amyl alcohol for Co-Ral in milk,[38] conversion of guthion to anthranilic acid which is extracted with benzene at its isoelectric point,[39] hydrolysis of DEF and steam distillation of the resultant mercaptan and purification by dialysis for the fluorometric analysis of gibberellic acid.[40]

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[37] MacDougall, D. (1963) in *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives, Volume I*, edited by G. Zweig, Academic Press, New York, pp. 167—188.

[38] *Ibid.*

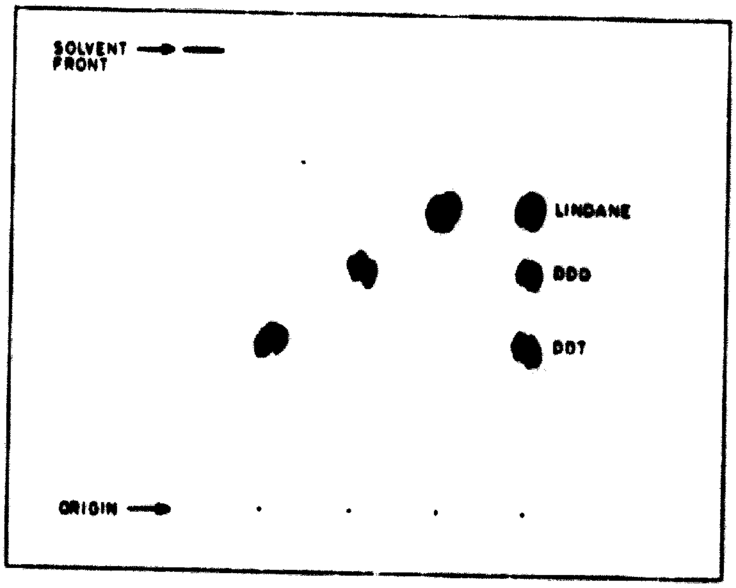
[39] *Ibid.*

[40] Tepe, J. B. and F. J. Holzer (1967) *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives, Volume V*, edited by G. Zweig, Academic Press, New York, pp. 413—422.

PAPER CHROMATOGRAPHY

By 1952, paper chromatography had become one of the most useful analytical tools for the separation and identification of a diverse group of chemical compounds and inorganic ions in microgram quantities. Reports appeared on the paper chromatography of amino acid, sugars, steroids, inorganics and almost any chemical compound, natural or synthetic, with the possible exception of hydrocarbons.[41] However, it was not until 1958 that Mitchell published his monumental work on the paper chromatographic separation of 114 pesticide chemicals.[42] The advances of Mitchell were the use of reversed-phase paper chromatography for fat-soluble pesticides and a sensitive spray reagent for the detection of chlorinated pesticides. The reagent was an acetone solution of silver nitrate and 2-phenoxyethanol. The sprayed paper chromatograms had to be exposed to ultra-violet light to reveal black spots due to colloidal silver, which indicated the position of chlorinated compounds. Mitchell had solved the problems of speed (1.25 to 2.5 hours for ten simultaneous analyses), sensitivity (less than 1 μg) and the resolution of closely related insecticides (see figure 3).

Figure 3. Paper chromatogram of mixed chlorinated pesticides



The detection of organophosphate insecticides was accomplished by using an enzyme spray (carboxylesterase from beef-liver homogenates) and 1-naphthyl acetate as the substrate spray.[43] Wherever the organophosphate insecticide had

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[41] Block, R. J., E. L. Durrum and G. Zweig (1958) *A Manual of Paper Chromatography and Paper Electrophoresis*, 2nd ed., Academic Press, New York, p. 710.

[42] Mitchell, L. C., *op. cit.*

[43] McKinley, W. P. (1963) *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives, Volume I*, edited by G. Zweig, Academic Press, New York, pp. 227—252.

migrated on the paper, the hydrolysis of the substrate was inhibited. Thus, when the chromatograms were subsequently sprayed with a diazo compound (Azoene Fast Blue RR salt) which reacts with 1-naphthol to give a brown dye, the phosphates appeared as white or yellowish spots on a dark background. The sensitivity of the detection was about 0.5 μg. Using a similar enzymatic detection method on thin-layer chromatograms, Menn and McBain[44] claimed that as little as 1 ng of some organophosphate insecticides could be detected (see below).

One of the first reported applications of paper chromatography to residue analyses was the detection of carbaryl in wine.[45] The wine samples are purified in this procedure using several solvent partition steps in order to remove waxes and pigments. The concentrated purified extract is chromatographed on untreated paper with a methanol-water solvent. The spray reagent (p-nitrobenzenediazonium fluoborate) is suitable to detect carbaryl and possibly metabolite 1-naphthol with a sensitivity of about 0.5 μg.

The first practical, general clean-up scheme for fruits, vegetables and dairy products published[46] in 1959 represented a real break-through in the development of pesticide residue methods which were faster, more general and sensitive than conventional spectrophotometric techniques. The innovation of the clean-up procedure was the use of acetonitrile-petroleum ether as partitioning agents for fats and fat-soluble pesticides, the latter being more soluble in the acetonitrile phase. The other modification was an additional clean-up step by column chromatography on Florisil. The final analytical step in the procedure was Mitchell's reversed-phase paper chromatography, which revealed unsuspected residues of chlorinated pesticides and their metabolites. These compounds appear to be the most stable and persistent residues found in many foods and dairy products and could not be detected by the older analytical methods.

Similar results were achieved for the separation and detection of phenoxyalkyl acid herbicides in wheat[47] by one- and two-dimensional paper chromatography. Semiquantitative estimation of pesticides can be achieved directly on developed paper chromatograms by visual comparison of known standards or by more sophisticated photoelectric densitometry.[48] Although paper chromatography is being displaced by even more rapid methods like thin-layer chromatography and more accurate methods like gas chromatography, paper chromatography retains its place as a simple, inexpensive and effective screening technique for the analyses of microgram quantities of pesticide residues in biological samples.[49]

THIN-LAYER CHROMATOGRAPHY

Paper chromatography for the resolution, detection and identification of pesticides has now been replaced to a great extent by thin-layer chromatography.

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[44] Menn, J. J. and J. B. McBain, *op. cit.*

[45] Zweig, G. and T. E. Archer (1958) *Journal of Agricultural Food Chemists*, Vol. 6, p. 910.

[46] Mills, P. A., *op. cit.*

[47] Yip, G. (1962) *Journal of the Association of Official Agricultural Chemists*, Vol. 45, p. 367.

[48] Block, R. J. *et al.*, *op. cit.*

[49] Coffin, D. E. (1966) *Journal of the Association of Official Analytical Chemists*, Vol. 49, p. 638; Mitchell, L. C. (1957) *Journal of the Association of Official Agricultural Chemists*, Vol. 40, p. 999.

The advantages of the latter technique are the use of untreated plates (versus the impregnation of paper with immobile phase), the greater speed of separation (20 minutes versus 150 minutes), better resolution ("tight" spots versus sometime elongated, diffuse spots) and greater sensitivity (10 ng versus 1 μg). In the first comprehensive report on thin-layer chromatography of insecticides, Walker and Beroza[50] studied 33 phosphate and 29 chlorinated pesticides. Silica gel G (with $CaSO_4$ as binder) at a thickness of 275 nm was used with chloroform, benzene or 1-hexane as solvents in combination with small quantities of polar liquids. The detection procedure consisted of a quick oxidation step with bromine vapours, followed by fluorescein spray, then a solution of silver nitrate that contains some phenoxyethanol and finally exposure to ultra-violet light.

The above method was adapted to residue analyses of pesticides in food[51] using a carefully cleaned-up sample as described in the above discussion of paper chromatography.[52] Pre-washing of aluminium oxide G (neutral) and silica gel G with distilled water to remove chlorides prior to coating of the plates increased the sensitivity of the method to 10 ng for many chlorinated insecticides. Table 5 lists migration values compared with the movement of DDD; an arbitrary R-value of 1.0 has been assigned to DDD.

TABLE 5. R_{DDD} VALUES OF CHLORINATED PESTICIDES SEPARATED BY THIN-LAYER CHROMATOGRAPHY

Pesticide	*1-heptane solvent*	
	A_2O_3G	*Silica gel G*
Aldrin	1.67	2.00
DDE	1.62	1.90
Heptachlor	1.59	1.74
DDT	1.41	1.45
Perthane	1.17	0.79
Lindane	1.03	0.48
DDD	1.00	1.00
Heptachlor epoxide	0.74	0.36
Endrin	0.54	0 22
Dieldrin	0.53	0.21
Methoxychlor	0.34	0.05
Kelthane	0.06	0.21

A thin-layer chromatography method for organophosphates, which is twenty times more sensitive than a comparable paper chromatography technique, involves the use of Al_2O_3 G-coated plates impregnated with N, N-dimethylformamide as stationary phase.[53] The mobile solvent is methylcyclohexane. The

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[50] Walker, K. C. and M. Beroza (1963) *Journal of the Association of Official Agricultural Chemists*, Vol. 46, p. 250.

[51] Kovacs, M. F. Jr., (1963, *Journal of the Association of Official Agricultural Chemists*, Vol. 46, p. 884.

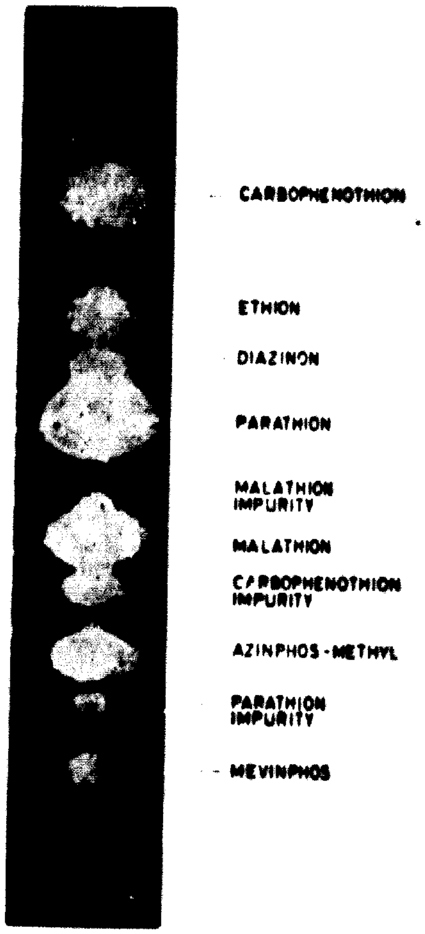
[52] Mills, P. A., *op. cit.*

[53] Kovacs, M. F. Jr., (1964) *Journal of the Association of Official Agricultural Chemists*, Vol. 47, p. 1097.

chromogenic spray reagents used in succession are tetrabromophenolphthalein ethyl ester, $AgNO_3$ and citric acid. Although the colour of the spots (blue-purple on yellow background) will fade within a short time, as little as 50 to 100 ng of common thionophosphate insecticides can be detected and estimated semi-quantitatively by visual inspection.

An even more sensitive thin-layer chromatography method detects as little as 1 to 10 ng of organophosphate insecticides.[54] The required adsorbent was cellulose powder without binder; silica gel or Florisil adsorbents were found to be unsuitable for this technique. An enzymatic spraying procedure consisted of successive treatments of human blood plasma spray (source of cholinesterase), incubation for 30 minutes and mixed spray consisting of bromthymol blue in dilute base and acetylcholine chloride. Blue spots on a yellow background indicated the presence of cholinesterase inhibitors but faded within 1 hour. A variation[55] of this procedure specified 5-bromoindoxyl acetate as the substrate indicator and resulted in blue spots on a white background (see figure 4).

Figure 4. Thin-layer chromatograms (Kieselgel G-HR) of organophosphate insecticides using an enzymatic spray and 1-hexane-acetone (8:2, volume/volume) solvent



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[54] Menn, J. J. and J. B. McBain, *op. cit.*

[55] Mendoza, C. E., P. J. Wales, H. A. McLeod and W. P. McKinley (1968) *Analyst*, Vol. 93, p. 173.

The ready availability of pre-coated, thin-layer plates on plastic films with a variety of adsorbents will undoubtedly popularize this technique for the routine analyses of pesticide residues.[56] Although there seem to be no published reports on their use for pesticide analysis, there is no reason to believe that this elegant technique would fail with the use of pre-coated films. A comparison was made on the separation of plant pigments by paper chromatography and by thin-layer chromatography on pre-coated cellulose sheets. Little difference in chromatographic behaviour was noted,[57] although the resolution on thin-layer plates was a little superior.

GAS CHROMATOGRAPHY

Gas-liquid chromatography flourished during the 1950s in the analyses of complex mixtures of chemically closely related homologues of fatty acids and hydrocarbons. It was not until 1959, however, that Coulson and co-workers published their classic paper on the separation of pesticides by gas chromatography.[58] The second paper on the subject appeared in 1960 and described the quantitative analysis of the two geometric isomers of endosulfan by gas chromatography.[59] The experiments were conducted isothermally at 250° C using a 6-foot (183 cm), $\frac{1}{4}$-inch (0.6 cm) diameter, stainless steel column, packed with 30 per cent by weight of Dow-11 high-vacuum silicone grease. Effluent fractions were detected by thermal conductivity with a catharometer at an absolute sensitivity of 25 μg based on an acceptable noise-signal ratio. Infra-red analyses of trapped-out fractions showed no isomerization or decomposition of endosulfan isomers.

These early experiments on the gas chromatography of organic pesticides illustrated the following significant findings about the instrumental analysis of pesticides, which were to usher in the new era of submicrogram detection of these compounds that is significant to agriculture and public health:

(1) The chlorinated pesticides usually have a high melting point (e.g. endosulfan A isomer 203° to 205° C) and could be put through a chromatographic column at a temperature of 250° C without significant decomposition;

(2) A mixture of related pesticides such as aldrin, dieldrin and heptachlor could be separated on a suitable column;

(3) The sensitivity of the method at that time was not satisfactory, and detectors with greater sensitivity had to be developed;

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[56] Wise, J. J. (1967) *Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives, Volume V*, edited by G. Zweig, Academic Press, New York, pp. 47—66.

[57] Sherma, J. and G. Zweig (1967) *Journal of Chromatography*, Vol. 31, p. 439.

[58] Coulson, D. M., L. A. Cavanagh and J. Stuart (1959) *Journal of Agricultural and Food Chemistry*, Vol. 7, p. 250.

[59] Zweig, G. and T. E. Archer (1960) *Journal of Agricultural and Food Chemistry*, Vol. 8, p. 190.

(4) The catharometer detector was non-selective and unsuitable for pesticide residue analysis in foods and crops due to interferences from extraneous substances present in much higher concentrations than the suspected pesticide residue.

The past ten years have seen great progress in more selected and sensitive detectors, and the gas chromatography instrument has become more sophisticated to give higher reliability and reproducibility. It is safe to guess the great majority of pesticide residues are analysed today by gas-liquid chromatography using detectors with the highest sensitivity (electron-capture) or selectivity (N, P, S or halogen). These advances are discussed below.

Columns and packings

Pyrex glass columns have largely replaced the older columns made of stainless steel, copper or aluminium. Metal columns tend to decompose some of the chlorinated pesticides, and glass columns are easier to fabricate into a variety of shapes and sizes. It is desirable to observe through the transparent walls of the column that the packing is uniform.

Anakrom ABS is an acid-base-washed siliconized solid support and is recommended for general use in pesticide analysis.[60] The preferred stationary phases are Dow-Corning-200 oil (10 per cent by weight) or a mixture of DC-200 and a fluorosilicone grease QF-1. Depending on the chemical nature of the pesticides to be analysed, the choice of the stationary phase may be a rational one (polar versus non-polar) or in some cases an empirical one.

To illustrate the empirical nature even in the choice of inert support, it was found[61] that methyl and ethyl parathion, and para-oxon could be resolved by QF-1 on Chromosorb G but not on Chromosorb W. Table 6 summarizes the choice of stationary phases coated on Anakrom ABS for several classes of pesticides.

TABLE 6. STATIONARY PHASES FOR GAS CHROMATOGRAPHY OF PESTICIDES

Pesticide	*Stationary phase*
Phosphate	**1—3% SE 30 (0.2% Versamid)** **10% DC 200**
Chlorinated	**10% DC 200**
Triazine herbicide	**5% Carbowax 20 M**
Pyrethrin	**5% SE 30 plus 5% QF-1**
Carbamate	**2% DC 200**
Phenoxyalkyl ester herbicide......	**20% DC grease**

Source: Lynn, T. R., C. L. Hoffman and M. M. Austin (1968) *Guide to Stationary Phases for Gas Chromatography*, Analabs, Inc., North Haven, Connecticut, pp. 56—60.

The support is Anakrom ABS.

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[60] Burke, J. A. (1965) *Journal of the Association of Official Agricultural Chemists*, Vol. 48, p. 1037.

[61] Bevenue, A. and F. Erro (1965) *Aerograph Previews and Reviews*, May issue, p. 6.

Combination methods for detection

First attempts to achieve selectivity by gas chromatography with non-selective detectors consisted of the preliminary separation of pesticides by GLC, followed by the analysis of condensed fractions. The following techniques are probably more of historical interest than of practical value, since in the meantime specific on-stream detectors for different classes of pesticides have been developed.

GLC-colorimetry[62]

Trace analysis of the herbicide amiben was accomplished by passing the methyl ester of amiben through a GLC column (Dow-11) at 275 ° C and collecting fractions two to five minutes after injection. The collected fractions were diazotized and coupled with naphthylethylenediamine and the resultant colour read at 528 nm. Standard curves of 2 to 15 μg amibengave straight lines.

A similar procedure was followed for the residue determination of the plant-growth regulator naphthaleneacetic acid in olives.[63] After a rigorous clean-up with acid-base extractions and silica-gel column chromatography, the final extract was treated with diazomethane to form the methyl ester and chromatographed at 210 ° C on Dow-11. Fractions were collected at the appropriate retention time of the methyl ester, and the nitrated products were measured with a spectrophotometer at 360 nm.

GLC—ultra-violet spectrophotometry[64]

Plant interferences from potatoes proved to be much less of a problem than for olives in the determination of naphthaleneacetic acid (NAA) and its methyl ester (MENA). Gas chromatographic conditions were identical to those described in the preceding method. The collected effluent fractions were dissolved in ethanol and absorbencies determined at two peaks in the ultra-violet region. The method yielded a sensitivity of 0.4 ppm with respect to the crop material.

GLC—infra-red spectrophotometry

Methods for residue analyses of endosulfan and organophosphate insecticides by infra-red spectrophotometry following GLC have been discussed above.

GLC of radioactive derivatives[65]

Residue analysis of the herbicide 2,4-D in field crops was carried out by gas chromatography of the ^{14}C-methyl ester of 2,4-D. Effluent fractions were collected directly into phosphor solution and counted by liquid-scintillation spectrometry. Background counts were reduced by acid-base washings and extractions and column chromatography on basic alumina. The final extract was treated with

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[62] Zweig, G. and R. E. Breidenbach, *op. cit.*

[63] Zweig, G., D. L. Gutnick, R. Gulli, T. E. Archer and H. T. Hartman (1964) *Journal of Agricultural and Food Chemistry*, Vol. 12, p. 59.

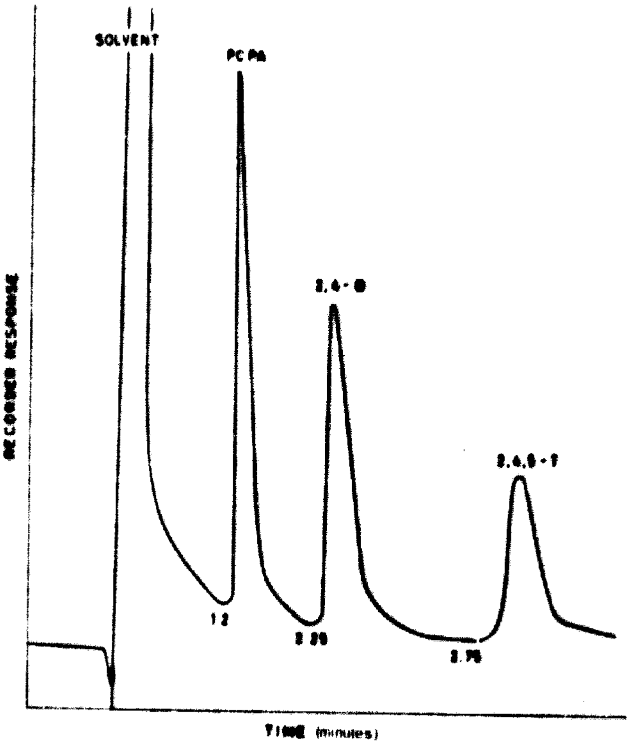
[64] Zweig, G., T. E. Archer and D. Raz (1962) *Journal of Agricultural and Food Chemistry*, Vol. 10, p. 199.

[65] Zweig, G. (1962) *Progress Report W-45*, University of California, Davis; Gutnick D. L. and G. Zweig (1964) *Journal of Chromatography*, Vol. 13, p. 319.

^{14}C-diazomethane and gas chromatography performed at 250° C on Dow-11. Fractions were collected at retention times between 2 and 6 minutes. The sensitivity of the method was 5 μg of 2,4-D, which corresponded to a net count of 2,000 counts/minute.

The radioactive derivative method was extended to the analysis of the three related phenoxyalkanoic acids 2,4-D; 2, 4, 5,-T and PCPA. The retention times were 1.2 minutes for PCPA, 2.25 minutes for 2,4-D and 3.75 minutes for 2,4,5-T. A fraction was collected for about 2 minutes duration close to the retention time (see figure 5).

Figure 5. Gas chromatography of three methyl ester herbicides on Dow-11 silicone high-vacuum grease at 210° C



Electron-capture detector

Probably the greatest single step in increasing the detectability of chlorinated pesticides was the development of the electron-capture detector by Lovelock and Lipsky.[66] In this technique, a radioactive, beta-emitting source ionizes the molecules of the carrier gas N_2 to produce slow electrons,[67] which migrate to the anode (see figures 6 and 7) under a fixed potential producing a steady current. If a compound is an electron absorber, the current is reduced and measures the quantity and electron affinity. The radioactive source may be tritium in the form of titanium tritide (figure 6) or ^{63}Ni for a high-temperature detector (figure 7).

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[66] Lovelock, J. E. and S. R. Lipsky (1960) *Journal of the American Chemical Society*, Vol. 82, p. 431.

[67] Dimick, K. P. and H. Hartmann (1963) *Varian Aerograph Technical Bulletin*, pp. 106–163.

The extent of electron affinity of various molecules is shown in table 7; CCl_4 has more than 400-billion times the electron affinity of hexane. It is seen that chlorinated compounds are efficient electron-capturing molecules and can serve as the basis for a sensitive detection of chlorinated pesticides.

TABLE 7. THE RELATIVE SENSITIVITIES OF THE ELECTRON-CAPTURE DETECTOR FOR ORGANIC COMPOUNDS

Compound	*D.U./μg*
Hexane	0.9
Heptane	1.2
Octane	1.5
Decane	2.6
Chlorobenzene	55
Atrazine	3,000
Dichloroethane	20,000
Lead tetraethyl	30,000
Benzophenone	100,000
2,4-D	125,000
Tedion	180,000
Malathion	250,000
Diethyl maleate	550,000
Thiodan	600,000
2,4,5-T	800,000
Kelthane (decomposition product)	1,600,000
DDD	2,000,000
DDT (para and para')	2,000,000
DDE	3,200,000
Heptachlor	4,800,000
Dieldrin	8,000,000
Endrin	8,000,000
Aldrin	10,000,000
Lindane	11,000,000
Dibromoethane	11,000,000
Fluothane	16,000,000
Carbon tetrachloride	400,000,000

The values are not necessarily optimum and do not represent ultimate sensitivity. They are based on practical detectability. The value D.U./μg is based on peak area measurement by a disc integrator using a 60 rpm motor. Each disc stroke is 100 disc units.

The first reported application[68] of the electron-capture detector for the analysis of pesticide residues in crops clearly demonstrated the following basic advantages of this technique over non-selective detectors: (high sensitivity 10^{12} g of lindane) and low background due to interferences from endogenous plant extracts. The sensitivity of electron-capture is illustrated in table 8 which lists the pesticides most amenable to this detector.[69] One-half full-scale deflection

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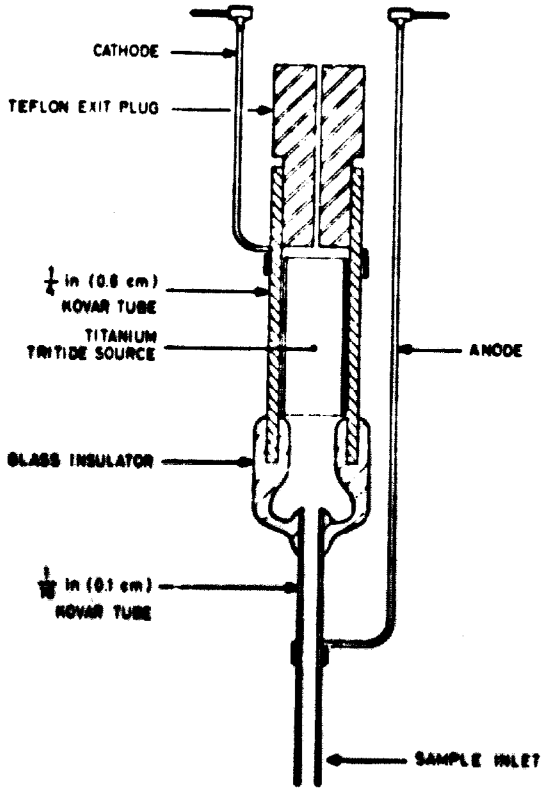
[68] Goodwin, E. S., R. Goulden, A. Richardson and G. G. Reynolds (1960) *Chemistry and Industry*, Vol. 39, p. 1220; Moore, A. D. (1962) *Journal of Economic Entomology*, Vol. 55, p. 271.

[69] Burke, J. A. and W. Holswade (1966) *Journal of the Association of Official Analytical Chemists*, Vol. 49, p. 374.

Figure 6. The Varian-Aerograph concentric-tube, electron-capture detector



(FSD) is produced by as little as 0.3 ng of lindane. On the other hand, this detector is not suitable for the herbicide CIPC or the insecticide Meta-Systox-R. The detectability can be increased by a factor of at least five by choosing $^{1}/_{10}$ FSD instead of ½ FSD as presented in table 8.

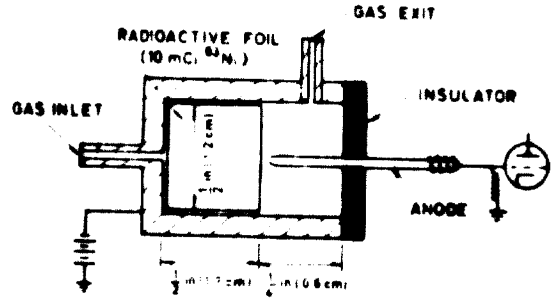
TABLE 8. RESPONSE OF PESTICIDES TO ELECTRON-CAPTURE DETECTION (TRITIUM SOURCE)

Pesticide	*Response ng for ½ FSD**
DDVP	2.0
sym-triazine	300
TCNB	0.5
2,4-D methyl ester	4.0
Lindane	0.3
Heptachlor	0.5
Aldrin	0.6
Chlordane	2.0
Meta-Systox-R	2000—3000
TEPP	5000
Endrin	2.5

* FSD – full-scale deflection.

However, electron capture is no panacea for the pesticide residue analyst. The plant extract containing the suspected pesticide residue must be thoroughly cleaned as discussed above. Excessive quantities of plant substances are usually present at much higher concentration than submicrogram and will be detected by electron capture; i.e. the detector is not specific for halogen-containing

Figure 7. High temperature electron-capture detector with ^{63}Ni source



molecules (see table 7). Plant extracts and bleeding of the stationary phase from the column cause the tritium detector to become contaminated and lose sensitivity due to lowering of the standing current. (In this event, the tritium foil can be cleaned by ultrasonic treatment.)[70] The latter problem has been partially resolved by using ^{63}Ni electroplated to a stainless steel foil.[71] After more than one year of continuous operation at 300° C with a Ni detector, there was no observable significant change in standing current or radioactive leakage.

Practical hints

A few basic rules for the successful analysis of pesticide residues in vegetables by gas chromatography with the electron-capture detector should be considered:[72]

(*a*) Keep applied voltage at less than maximum sensitivity to reduce background signals from crops and solvents.

(*b*) Use electrometer setting where linearity of response is obtained. Use pre-purified nitrogen and keep detector (tritium) temperature at 200° C.

(*c*) Use pre-conditioned (4 to 5 days at 250° C) column of 10 per cent DC 200 on Anakrom ABS for chlorinated pesticides. Condition the column further by injecting milligram quantities of pesticides.

(*d*) Sample clean-up should be thorough and follow the procedures described above. Acetonitrile and petroleum ether should be redistilled in glass. Keep away from polyethylene containers and bottle caps!

Quantitative analysis

Quantitative determinations of pesticides based on retention curves are related to standards put through the gas chromatograph. The only absolute method based on microcoulometry is discussed below. A detailed study[73] has revealed that the following six different methods of calculation yielded comparable results:

(*a*) Peak height alone is used for slim peaks, but operating parameters must be held closely;

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[70] Dimick, K. P. and H. Hartmann, *op. cit.*

[71] Ahren, A. W. and W. F. Phillips (1967) *Journal of Agricultural and Food Chemistry*, Vol. 15, p. 647.

[72] Burke, J. and L. Giuffrida (1964) *Journal of the Association of Official Analytical Chemists*, Vol. 47, p. 326.

[73] Gaul, J. A. (1966) *Journal of the Association of Official Analytical Chemists*, Vol. 49, p. 389.

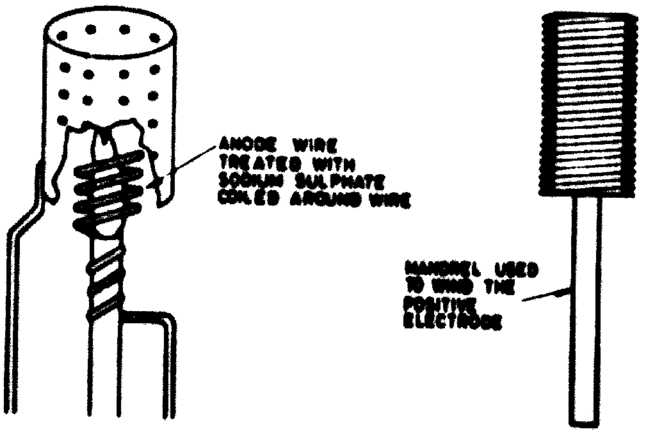
(*b*) Product of peak height and width of the peak at half-height;
(*c*) "Area" as a product of retention time and peak height;
(*d*) Cutting out and weighing the peaks;
(*e*) Mechanical or electrical integrator attached to recorder;
(*f*) Triangulation (a triangle is constructed by inflectional tangents to form an apex).

If peaks are not resolved, symmetrical curves are drawn; sloping base lines are drawn by connecting the lowest point of deflection. Even with all of the imperfections of resolution, experimental pipetting errors and interfering peaks, it is not too difficult to obtain quantitative data with a deviation not greater than 2.5 to 6.0 per cent.

Flame ionization detector for phosphorus

As discussed above, selective detection of organophosphate insecticides was not greatly improved by the electron-capture detector. An important discovery was made simultaneously by Karmen[74] and Giuffrida[75] who demonstrated that different alkali metals in the hydrogen-flame ionization detector enhanced the response from halogen- and especially phosphorus-containing compounds. The explanation of Karmen[76] for this phenomenon was that compounds containing a halogen and phosphorus reacted with the metal probe to increase the rate of release of the metal. The resultant vapour was excited and ionized, thus increasing the electrical conductivity of the flame. Giuffrida[77] named this special flame ionization detector "sodium thermionic detector". The construction of the detector was a slight modification of a standard hydrogen-flame ionization detector by replacing the positive electrode with a platinum-iridium coiled wire coated with Na_2SO_4 (figure 8). A graphic illustration of the selectivity of the thermionic detector is seen in figure 9. A mixture of a chlorinated compound

Figure 8. Modification of the standard hydrogen-flame ionization detector to construct a sodium thermionic detector



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[74] Karmen, A. (1964) *Analytical Chemistry*, Vol. 36, p. 1416.

[75] Giuffrida, L. (1964) *Journal of the Association of Official Analytical Chemists*, Vol. 47, p. 293.

[76] Karmen, A. (1965) *Journal of Gas Chromatography*, Vol. 3, p. 336.

[77] Giuffrida, L., *op. cit.*

Figure 9. Analysis of lindane, parathion and methyl stearate by hydrogen-flame ionization and sodium thermionic detectors

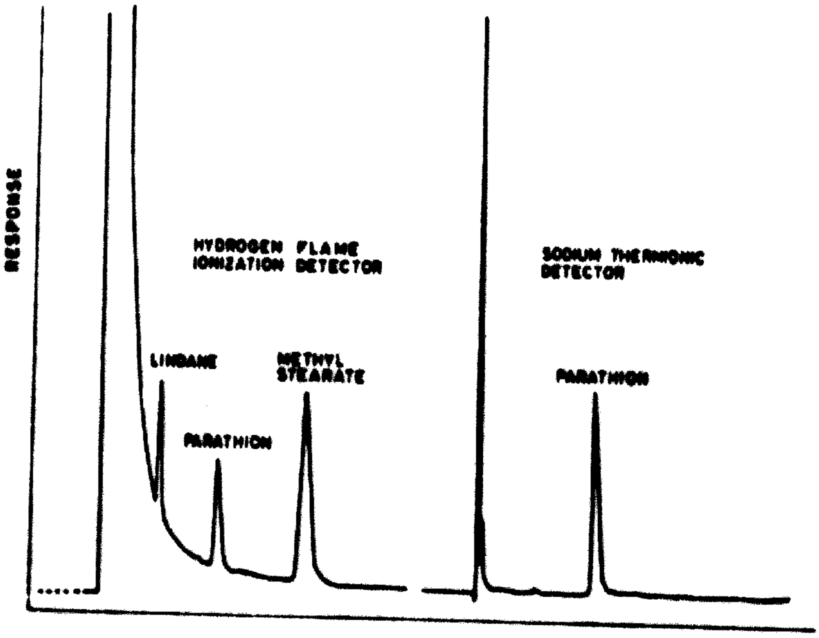
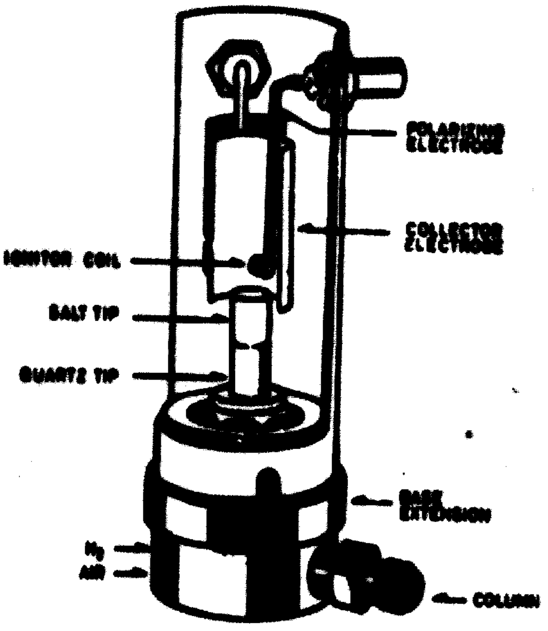
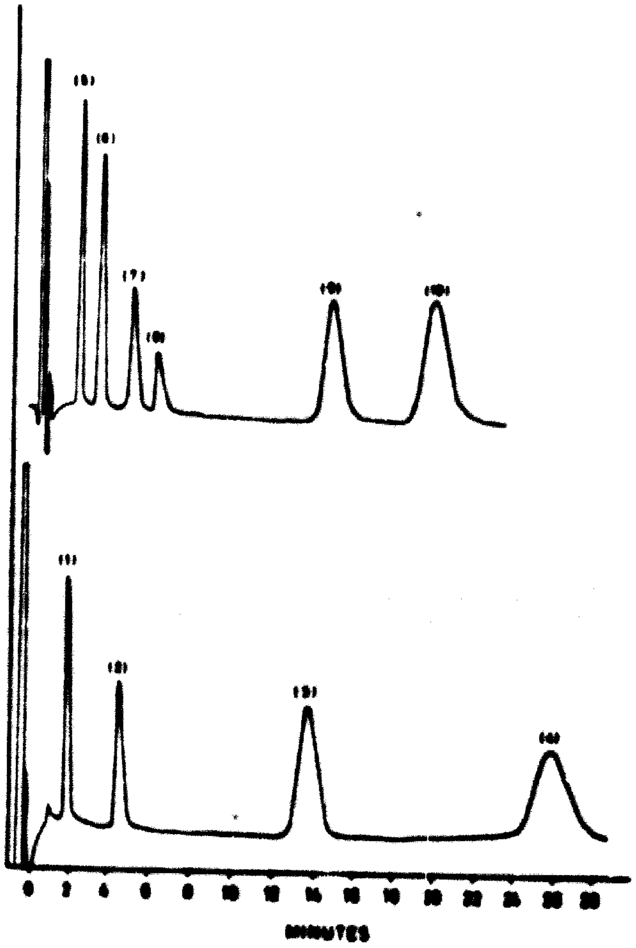


Figure 10. Cross-sectional sketch of the Varian-Aerograph thermionic detector



Source: Oaks, D. M., K. P. Dimick and C. H. Hartmann (1966) *Varian Aerograph Technical Bulletin*, W-122, p. 13.

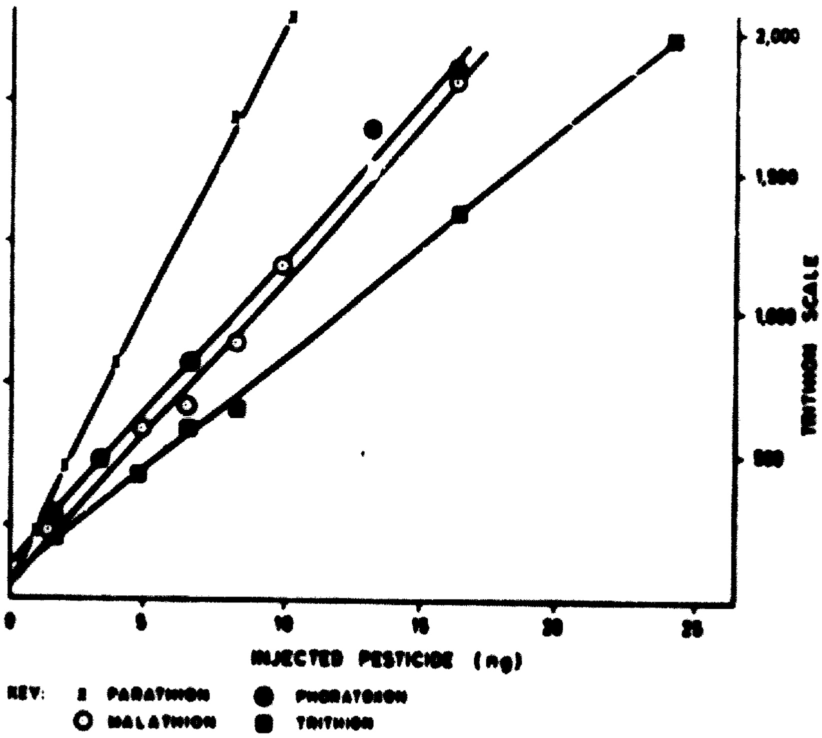
Figure 11. Response of thermionic detector to organophosphorus pesticides



Note: The column is 5 per cent SE-30 on 60/80 chromosorb W.

Key:
(1) 5 ng diazinon
(2) 5 ng parathion
(3) 10 ng ethion
(4) 20 ng EPN
(5) 5 ng thimet
(6) 5 ng Di-Syston
(7) 5 ng ronnel
(8) 20 ng malathion
(9) 40 ng methyl trithion
(10) 20 ng trithion

Figure 12. Standard curves of four insecticides showing the linearity of the thermionic detector response



(lindane), organophosphate (parathion) and hydrocarbon (methyl stearate) was resolved by gas chromatography and all three compounds were detected by the hydrogen-flame ionization detector, but only parathion was detected by the sodium thermionic detector at a three-hundredfold attenuation.

An improved version of the phosphorus detector developed by Varian-Aerograph is shown in figure 10. This is a modification of the commercial hydrogen-flame ionization detector with the addition of a salt tip made from a pressed pellet of caesium bromide. The phosphorus detector requires a carefully regulated flow of air and hydrogen. The response of the phosphorus detector is shown in figure 11 depicting the separation of two mixtures of organophosphate insecticides containing 5—40 ng of each component as indicated. The linearity of the phosphorus detector may be seen in figure 12 showing standard curves of three organophosphate insecticides and one metabolite ranging from 2—25 ng; trithion gives a significantly higher response than the other compounds. Many organophosphate insecticides may be detected at a sensitivity of 0.5 ng to 1.0 ng at 10 per cent of full-scale recorder deflection and a corresponding noise level of 5 per cent.[78] When helium was substituted as carrier gas in place of nitrogen, the sensitivity for phosphorus-containing pesticides was increased eightfold[79] with a potassium thermionic detector.

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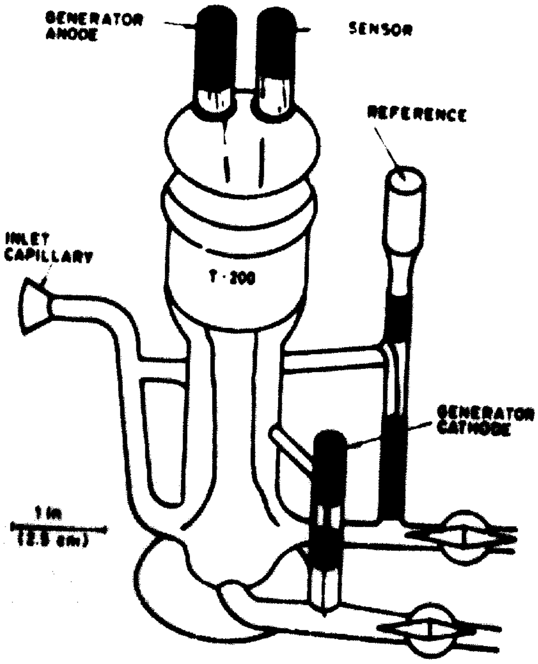
[78] Ruzicka, J., J. Thomson and B. B. Wheals (1967) *Journal of Chromatography*, Vol. 30, p. 92.

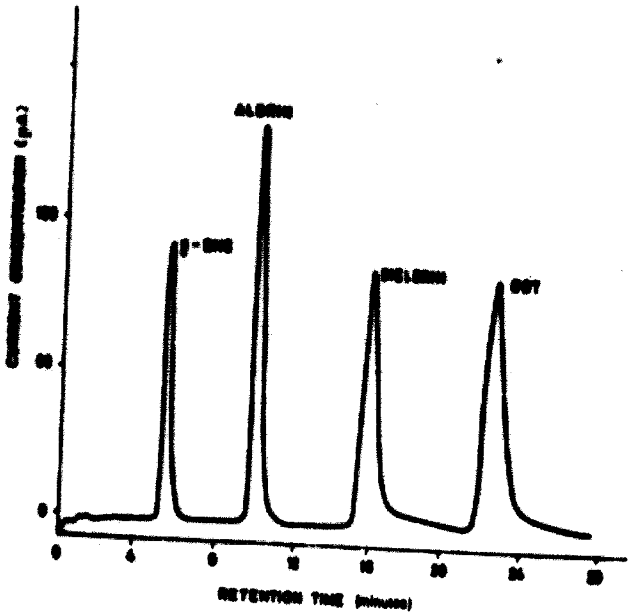
[79] Ford, J. H. and M. Beroza (1967) *Journal of the Association of Official Analytical Chemists*, Vol. 50, p. 601.

Figure 13. Model T-200 microcoulometric titration cell



Source: Cassil, C. C. (1962) *Residue Reviews*, Vol. 1, p. 37.

Figure 14. Microcoulometric gas chromatogram of a pesticide mixture



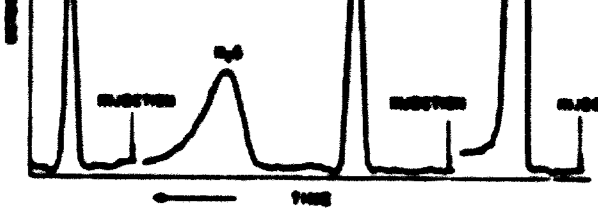
Note: The temperature is 252° C. The helium flow rate is 1 ml/sec. The 6 ft. (1.8 m) column is 20 per cent silicone grease on a 40/60 chromosorb mesh. The recorder has a 10 mV ordinate at 0.5 in/min. Its attenuation factor is 8.

Source: Coulson, D. M. *et al.* (1960) *Journal of Agricultural and Food Chemistry*, Vol. 8, p. 399.

Microcoulometric gas chromatography

Coulson *et al.* pioneered the gas chromatographic separation of pesticides and developed an ingenious microcoulometric gas chromatography system.[80] In it, the gas chromatography column is connected to a combustion tube furnace under oxidizing (for halogen) or reducing conditions[81] (for phosphorus). The gasses are then passed into a coulometric detector where halides (except F^-) and SO_2 are titrated with silver ions which are electrically generated. The titration cell is shown in figure 13; the reference electrode for a halide is a Ag/Ag^+ cell and for SO_2 the reference electrode is a platinum-I_2 couple.[82] The coulometer is based on a continuously balancing system in which the titrating agent is kept at a fixed concentration during the titration. When a sample enters the titration cell, the electrical current used to maintain a constant silver concentration is recorded as a function of time that results in a normal graphic representation of retention curves (figure 14). The area underneath the titration curve is proportional to the number of silver ions generated and can be related theoretically by Coulomb's law to the absolute quantity of pesticide which passed through the gas chromatographic column. This is a real advantage of microcoulometric gas chromatography over other detectors. Another advantage of the system is that as long as endogenous plant constituents do not alter the gas chromatographic behaviour of the pesticides under investigation, the sample clean-up is greatly simplified. The reason is that only a halide or sulphur is detected, and both elements are rarely found in an organic solvent extract from biological materials. The sensitivity of microcoulometric gas chromatography ranges from 0.1 μg tp 0.9 μg depending on the sulphur and chlorine content of the respective pesticide.

Figure 15. The microcoulometric chromatography of ronnel



Key: (A) Carrier gas passing into the titration cell; (B) with chromatographic tube of silica gel; (C) with subtraction tube of aluminium oxide.

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[80] Coulson, D. M., L. A. Cavanagh, J. E. DeVries and B. Walther (1960) *Journal of Agricultural and Food Chemistry*, Vol. 8, p. 399.

[81] Challacombe, J. A and J. A. McNulty (1964) *Residue Reviews*, Vol. 5, p. 57.

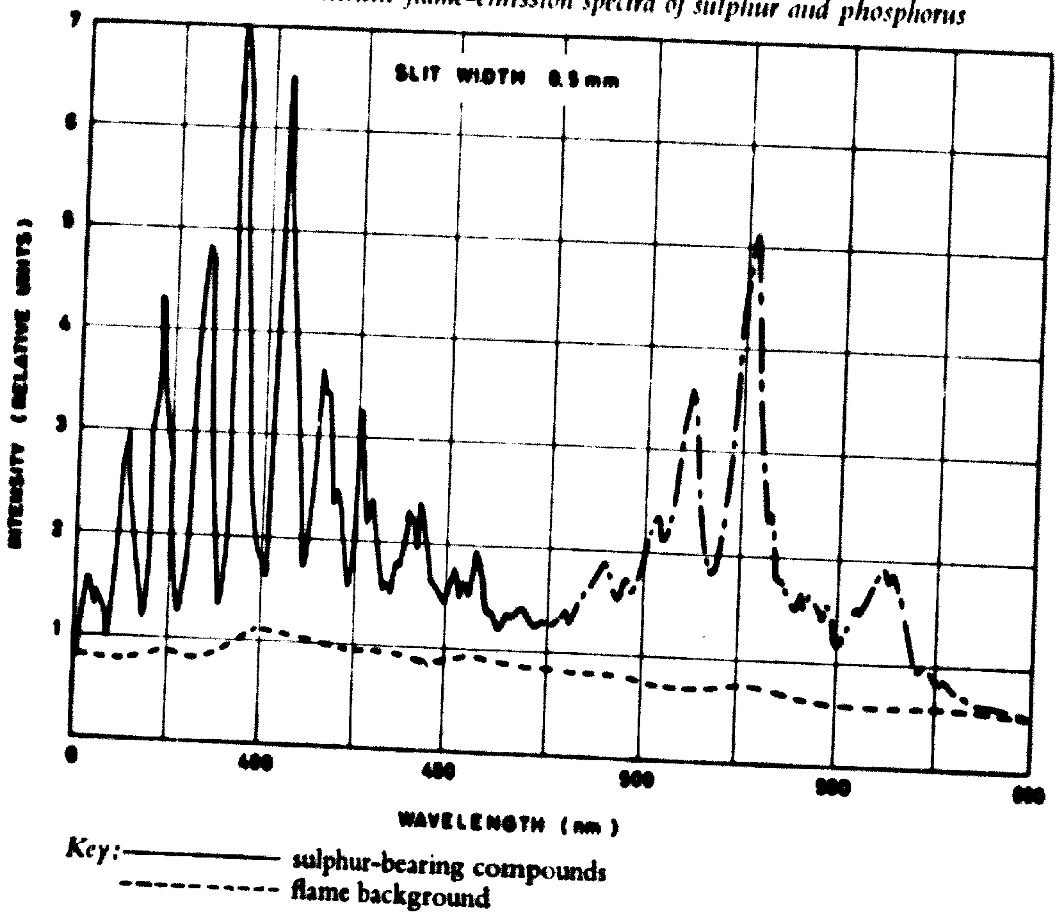
[82] Burchfield, H. P. *et al.*, *op. cit.*

A modified microcoulometric gas chromatography system[83] employs a reducing atmosphere at 950° C following separation on the column. The conversion products which are titrated coulometrically with silver ions are phosphine, hydrogen sulphide and hydrogen chloride. Thus, if a pesticide contained sulphur, phosphorus and chlorine, all three elements would be measured simultaneously. However, a short Al_2O_3 tube inserted between the reduction tube and titration cell removes H_2S and HCl leaving PH_3 to be titrated. Conversely, placing a short chromatographic tube of silica gel in the same position removes HCl and chromatographs PH_3 and H_2S. This principle is illustrated in figure 15 which depicts the gas chromatography of ronnel [0,0-dimethyl 0-(2,4,5-trichlorophenyl) phosphorothioate] and the insertion of the subtraction and chromatography tubes.

Flame photometric detector

Although the thermionic detector preferentially responds to phosphorus-containing compounds, a significant signal is produced by chlorinated organics. The sulphur detector by microcoulometry is not suitable for subnanogram quantities. Therefore, a significant advance was the new technique of flame photometry in a hydrogen-rich flame[84] for the specific detection of organophos-

Figure 16. Characteristic flame-emission spectra of sulphur and phosphorus



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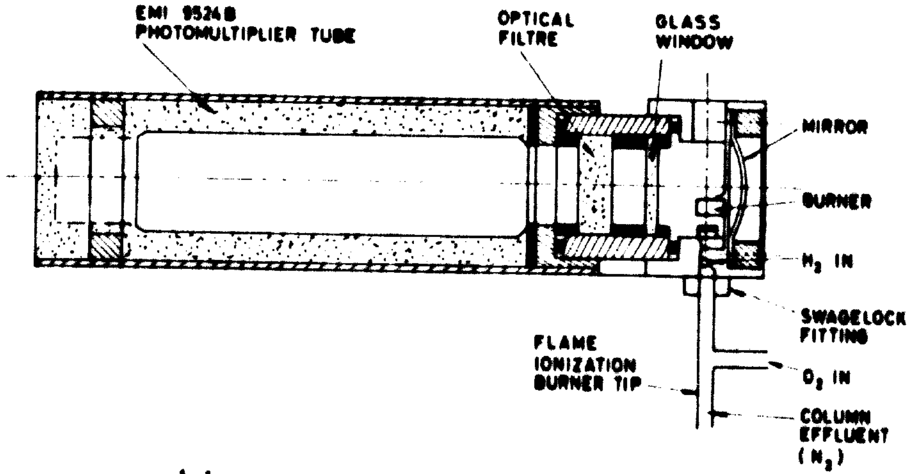
[83] *Ibid.*

[84] Brody, S. S. and J. E. Chaney (1966) *Journal of Gas Chromatography*, Vol. 4, pp. 42—46.

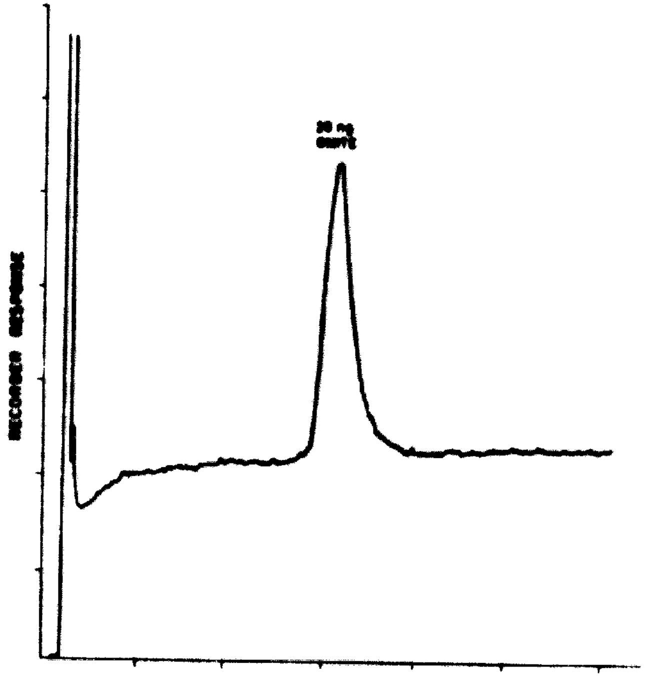
Figure 17. The flame-photometer detector



phate or organosulphur compounds at subnanogram levels. When sulphur or phosphorus is present, a characteristic flame emission occurs which can be separated easily by narrow-band interference filters (figure 16). The filters used are 394 nm for sulphur and 526 nm for phosphorus. The emitted light is shielded from interfering substances by an optical arrangement whereby only the sulphur and phosphorus compounds are burnt in the hydrogen-rich flame in direct view of the photomultiplier (figure 17).

To test the sensitivity and specificity of the flame-photometer detector, the pesticide omite, which contains sulphur, was chromatographed with a commercial isothermal gas chromatograph connected to the detector with the 394 nm filter. As is seen in figure 18, over 30 per cent FSD was achieved with 20 ng of

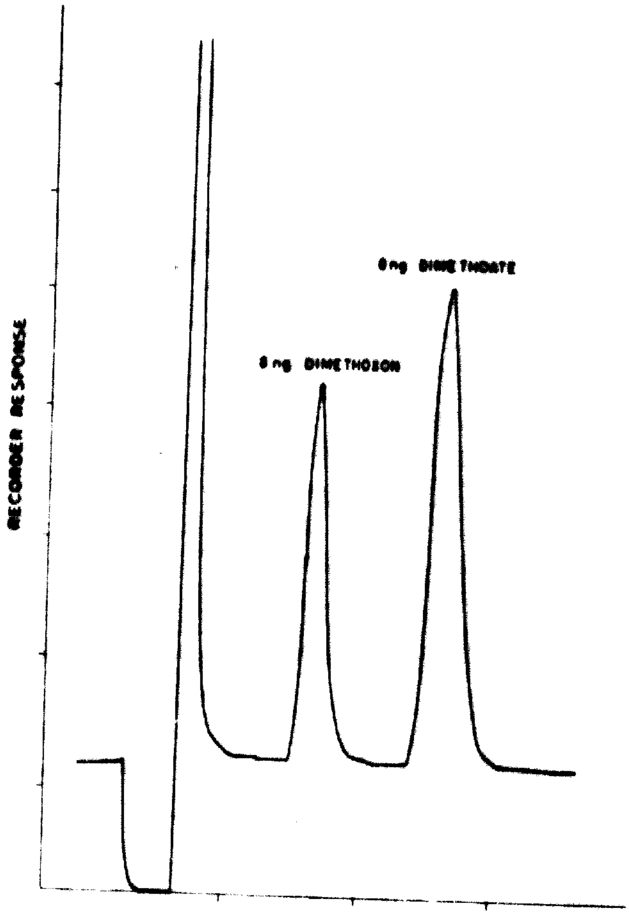
Figure 18. Gas chromatography of 20 ng omite in 2 per cent Se-30 on Anakrom ASB at 190°C



Note: The flame-photometer detector is in the sulphur mode with a 394 nm filter.
Source: Devine, J. M. (1969) Uniroyal Company and Syracuse University Research Corporation, unpublished results.

omite. Preliminary results from residue analyses of a variety of crops indicate a minimum of clean-up necessary for interference-free analysis. With the phosphorus filter in place, 8 ng each dimethoate and its oxygen analogue gave excellent response as is seen in figure 19. The one deficiency of the present commercial detector for operation below 150° C due to the plastic housing has been corrected by the insertion of a heat barrier, which increases the effective temperature of the detector to 270° C. A dual-channel flame photometer detector has been developed recently; it simultaneously detects sulphur and phosphorus from the same molecule on two separate chart recorders. A careful analysis of the response ratios may give important information on the identification of unknown pesticide metabolites.[85]

Figure 19. Gas chromatography of dimethoate and its oxygen analogue in 11 per cent DC-200 and 0.01 per cent versamid on gas chrom Q at 150° C



Note: **The flame-photometer detector is in the phosphorus mode with a 526 nm filter.**

Source: Devine, J. M. and N. R. Pasarela (1969) American Cynamid Company and Syracuse University Research Corporation, unpublished results.

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[85] Bowman, M. C. and M. Beroza (1968) *Analytical Chemistry*, Vol. 40, p. 1448.

Electrolytic conductivity detector

Many pesticides contain nitrogen, for example the symmetrical triazines or parathion. Until recently there was no gas chromatographic detector for nitrogen until Coulson developed the electrolytic conductivity detector (see figure 20).

Figure 20. Electrolytic conductivity detector

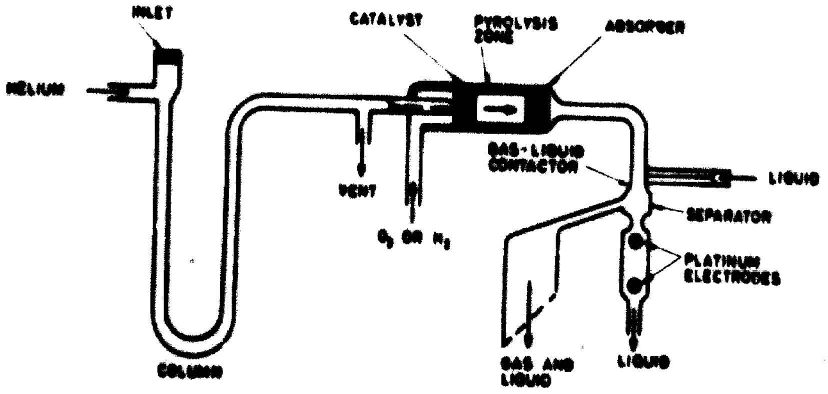
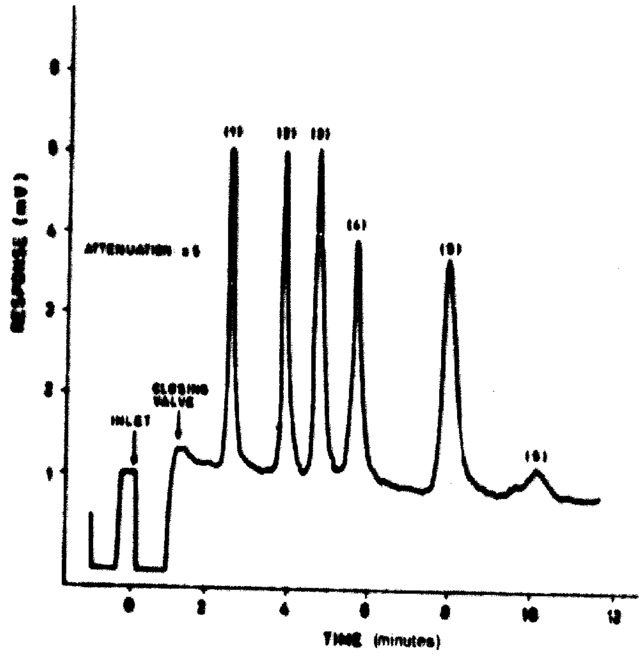


Figure 21. Electrolytic conductivity gas chromatogram



Note: Column: 12 per cent SE 30 on 80/100 mesh gas chrom Q, inner diameter 6 ft (1.8 m) × 4 mm; Column temperature: 220° C; Inlet, transfer line and venting valve temperature: 230° C; Oxidative furnace temperature: 850° C; Carrier gas—helium at 120 cm^3/minute; Pyrolysis gas—moist oxygen at 60 cm^3/minute.

Key:
(1) 10 ng lindane
(2) 20 ng heptachlor
(3) 20 ng aldrin
(4) 20 ng heptachlor epoxide
(5) 30 ng dieldrin
(6) 40 ng DDT

In the operation of this system, the effluent fractions from the gas chromatography column are passed through the pyrolizer in a hydrogen atmosphere with a nickel-wire catalyst converting organic nitrogen to ammonia. Interfering pyrolytic acid products are absorbed on strontium hydroxide, and ammonium ions are detected by measuring the change in conductivity between two platinum electrodes. The sensitivity of this detector is about 25 to 50 ng but the selectivity is excellent. In the oxidative mode-of-operation, the conductivity cell measures chloride ions with little interference from CO_2 due to its inability to dissolve rapidly in the water during its passage through the detector and its slight degree of ionization.[86] As is shown in figure 21, 10 to 40 ng of chlorinated pesticides are well resolved and detected by this gas chromatographic system coupled to an electrolytic conductivity detector.

Summary of chromatographic systems

Table 9 summarizes the detection range for the chromatographic systems discussed above. Although the electron-capture detector is the most sensitive detection system, its specificity is not as great as that of the other detectors. In the author's experience, the flame-photometry detector[87] is the most reliable instrument. Microcoulometric gas chromatography in the hands of experienced analysts for the determination of chlorinated and sulphur-containing pesticides is probably the method of choice.

TABLE 9. APPROXIMATE WORKING SENSITIVITY OF SELECTIVE DETECTORS

Detector	*Detected*	*Range*
Microcoulometer	Cl, Br, I, S and P	0.1—1 µg
Electron capture	Chlorinated	0.1—1 ng
Sodium thermionic	P	1.0—10 ng
Flame photometer	P and S	1 ng
Electrolytic conductivity	Chlorinated or Ni	10—100 ng

CONCLUSIONS AND SUMMARY

An attempt has been made to review the evolution which has taken place in the analysis of minute quantities of pesticide residues in food and crops. The zero tolerance established by governmental enforcement agencies was based on a scientific concept which was impossible or at best unnecessary to achieve. And yet, the zero tolerance gave the incentive to the ingenious pesticide residue chemist to devise more sensitive and selective methods of analysis. Thus, when chemists started seriously in the middle 1940s to analyse for DDT and parathion,

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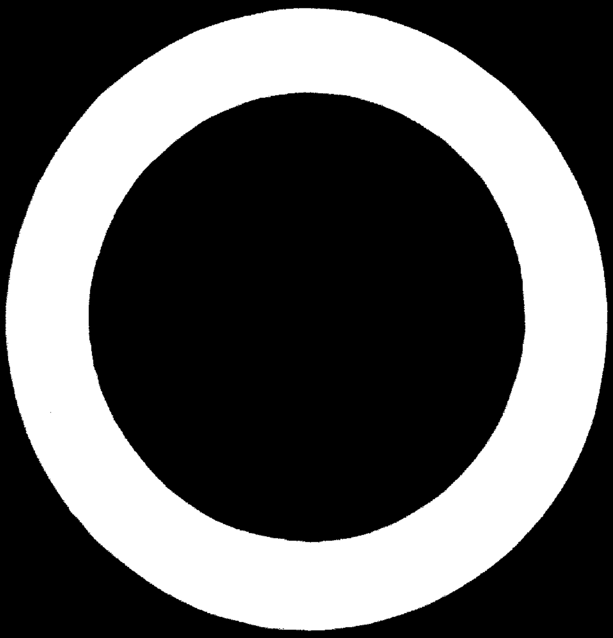
[86] Coulson, D. M. (1965) *Journal of Gas Chromatography*, Vol. 3, pp. 134—137.
[87] Brody, S. S. and J. E. Chaney, *op. cit.*

the limit of detectability was in the microgram range. Twenty years later, the sensitivity had been improved by a factor of 1 million.

Progress in pesticide analysis in the next decades will no longer be in the search for the proverbial zero as may be suggested by the line of progress depicted in figure 1, but it will rather be in devising methods of greater selectivity and the development of methods of positive identification of nanogram quantities of pesticide residues. The reader should have become aware that the tremendous increase in sensitivity of detection, as for example by electron-capture gas chromatography, has aggravated the problem of mistaken identity of chromatographic peaks. Absolute methods of identification, as for example gas chromatography coupled to mass spectrometry, are not within the financial capability of modestly equipped and funded laboratories. However, this equipment should become more readily available in the next ten years.



5. ESTABLISHMENT OF A PESTICIDE LABORATORY

*by Kenneth K. Krausche**

A venture into pesticide research in a developing country should be designed to stimulate the agricultural and industrial development of the country, to help satisfy the food and fibre needs of the people and to contribute to the economic well-being of the nation. It follows that any specific project design and plan of operation will vary in accordance with local problems and requirements.

A pesticide laboratory in almost any conceivable situation in a developing country should include among its first and primary functions the investigation and development of local resources for the formulation of pesticides and testing the effectiveness of pesticides in the laboratory and in the field under local conditions. If pesticide products are already being formulated or will be formulated, or if pesticide chemicals are already being manufactured or will be manufactured, the laboratory should be able to provide technical advice on the processes involved. The laboratory will have to advise on optimum conditions of application of the finished products, so that they fulfil the purpose for which they are designed in a safe, efficient and economical manner. The responsibilities of the laboratory will include establishment of product specifications and probably a role in regulation, registration and certification of pesticides.

Since this kind of research and development laboratory has a practical slant, the question of production control by the laboratory may arise. The answer will depend on the available production facilities and the available laboratory facilities in the production and formulating plants. In general, it is better for the production control laboratory and the research and development laboratory to be in separate but co-operating units.

REQUIREMENTS

The basic requisites of the laboratory will include personnel on all levels, physical facilities (that is, a place to work) and laboratory equipment (instruments, reagents and supplies). The required investments in manpower, facilities and equipment will vary widely. The following discussion describes some typical project needs based on a hypothetical average situation.

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* Food and Agriculture Organization of the United Nations, New York.

Personnel

The project manager must be a highly competent individual, who preferably is outstanding both as a pesticide chemist and as an administrator. The minimum scientific staff should include a formulations chemist, a pesticide analytical chemist, an insect toxicologist and one or more specialists in entomology, plant pathology and plant physiology depending on local needs.

The role of the formulations chemist will be described below. The analytical expert will carry great responsibilities in the project in the macro-determination of percentage composition of technical products, raw materials and finished formulations as well as in the micro-determinations of pesticide deposits on treated crops and residues on and in raw agricultural commodities. The insect toxicologist will play an important and practical role in determining the incidence, nature and causes of resistance to insecticides by insect pests and in deciding how to combat resistant strains in the field, if and when they occur.

The specialists in entomology, plant pathology and plant physiology will be faced with the practical problems of controlling the insect pests, the plant diseases and the weeds. Rats and certain other rodents cause grave losses in the food supply all over the world. Possibly the hypothetical laboratory should have a specialist in the use of rodenticides and in the application of other methods of rodent control, who can investigate the local problems and design practical control procedures.

Other staff may include a specialist in biometrics and an instrument engineer or technician. The biometrics expert will function not only in the mathematical and statistical interpretation of data derived from biological experiments, but more importantly, in the design of experiments so that derived data will be statistically significant. Because instrumentation is now an essential part of chemical analytical procedures, an instrument expert should prove valuable by maintaining the instruments in proper condition. Often, much time and production can be lost when instruments break down and expert help as well as parts and tools may not be available for their repair.

In an internationally sponsored project the foregoing types of specialists are usually recruited by the sponsoring agency. There will be counterpart individuals assigned by the host government for each of the internationally recruited experts. Whether the project is internationally sponsored or entirely a national institution, many more scientific personnel may be assigned depending on their availability. In addition, technicians, assistants, office help and manual labourers will be required. A well qualified administrative officer is required to expedite procurement of local supplies, to correlate office procedures and building services, and to supervise local office and service personnel.

Training of personnel will have to be an integral part of the laboratory plan of operation. In addition to trained scientific personnel, various other levels of training are important. Scientists may receive their formal education and gain their skills in their home countries, or they may have the opportunity to continue their education and gain expertise in pesticide specialities in foreign countries through fellowships or other arrangements. But a working project needs trained technicians, who can assist scientists and thus allow more efficient use of scarce scientific manpower. In developing countries, the need for skilled or semi-skilled technicians should not be overlooked; dependable personnel must be able to dely and adequately handle reagents, equipment and simple instruments, count samples, measure, weight and draw significant samples. Trained technicians can assume greater responsibility as they gain skill and, therefore, should enjoy incentives and prestige beyond those of the errand boy.

Physical facilities

The building or buildings for the project may be renovated structures or they may be newly constructed. A greenhouse, an insectarium and controlled-environment chambers may be required. Adequate provisions must be made for power and maintenance services for the operation of the laboratory.

Some countries may be able to supply a good portion of their own needs. However, usually the machinery, formulation equipment, reagents, glassware, scientific apparatus, instruments, control room and greenhouse equipment, fume hoods, and books and journals for the library must be imported. The journey of the glass apparatus and analytical and electronic equipment over land and sea is expensive, time-consuming and hazardous; it has not been unusual to find evidence of rough handling as well as an appalling breakage of equipment. This kind of damage might be avoided if the project management is able to arrange through the appropriate government officials for special supervision and special handling of its incoming crates and packages at the docks and en route to the laboratory.

Safety

Very early in the planning stage of the project, serious thought must be given to safety.[1] In ordering supplies for the project, the usual laboratory safety equipment, such as goggles, rubber gloves, aprons and similar items, should be included. The installation in the laboratory of fire extinguishers and safety sprinklers with quick-opening valves and drenching shower heads must not be overlooked. First-aid equipment and facilities for personal cleanliness must be provided.

Many pesticides are highly toxic to man, but these hazards can be controlled if handled carefully and knowledgeably. When highly toxic pesticides are involved, disposal of laboratory residues and wastes presents a special problem. This is especially true when relatively large quantities may be present, such as in the effluents from a pilot plant or small-scale production unit. Wastes and effluents may require special handling, such as chemical treatment or bio-degradation in holding basins designed for that purpose. Other methods consist of special incineration or disposal by burial in a sanitary landfill area set aside for the sole purpose to receive such wastes. Even the empty containers of some of the pesticide materials require special handling and disposal. If problems of disposal are an-

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[1] See also chapters 8 and 10.

ticipated or if compounds are involved whose possible side effects on man and the environment are not clearly understood, expert consultation should be provided. Personnel must be protected and adverse effects on the environment must be prevented.

Project management will have to emphasize the necessity for safety to all personnel connected with the project. The understanding of safety and the attitude toward prevention of accidents may not be as prevalent as in some highly developed industrial countries. Improvement in this situation calls for education and patience. Probably one of the first steps should be the formation of a safety committee by staff members. The committee should establish and implement a practical safety programme including enforcement of a simple fundamental code of essential rules of safety.

SCOPE OF THE PROGRAMME

In setting up the actual research projects and planning the investigations, it would be advisable to carefully look about the country—outside the immediate sphere of the laboratory—for additional sources of technical assistance and opportunities for technical co-operation. It may be possible to establish certain joint and mutually beneficial projects between the pesticide laboratory and technical groups already in existence. For example, certain investigations in mammalian toxicology may be carried out co-operatively with a veterinary group. As another example, studies of grain fumigation problems may be made jointly with a grain storage department, which may already have the required silos, bins and other specialized facilities.

Through co-operative joint programmes, the scope and range of research investigations can be increased and the need for duplication of costly, specialized and infrequently used equipment can be avoided. Furthermore, more efficient use can be made of the equipment and of the specially trained and experienced technicians required to operate it. Therefore, co-operative technical investigations are recommended as a means of expanding the useful scope of the laboratory project.

Another opportunity to expand the scope and utilitarian value of a national pesticides laboratory can arise from consideration of the common agricultural problems in a group of neighbouring countries. This may lead to a decision that the national laboratory scheme should evolve into a regional laboratory, thus increasing its operating base and its capacity to be of service.

6. PRINCIPLES OF PESTICIDE FORMULATION

by John Flanagan *

Pesticide formulation is the process of transforming a pesticidal chemical into a product which can be applied by practical methods to permit its effective, safe and economical use. It is not the intent in this chapter to present a compendium of recipes and cookbook procedures whereby different types of formulations can be made. To attempt this would be outside the scope of the present publication as well as totally misleading. There must be a practical and realistic objective and procedure for developing any pesticide formulation. A presentation of the principles and guide-lines of pesticide technology will be of practical use to those engaged in the development, manufacture, testing and use of pesticides.

The material presented here is the result of efforts by many workers in government and private industry. Although synthetic organic pesticides have attained spectacular success since their introduction in the middle 1940s, all specialists in pesticide formulation recognize that the technology is still highly empirical and primitive.

THE PESTICIDE FORMULATION

Definitions

A pesticide formulation is a physical mixture of one or more biologically active chemicals with inert ingredients which provides effective and economic control of pests. Because the great majority of all pesticidal chemicals require formulation to be used economically and effectively, the term "pesticide" throughout this chapter will refer to the finished product rather than to the active ingredient itself. Indeed, to the majority of the users of pesticides, the term pesticide is accepted as the total form of the finished product. Pesticide formulation is the art and technology of developing a formulation of a pesticide. A pesticide formulation plant is a manufacturing facility in which pesticidal ingredients are formulated into a final product.

Pesticide formulations are classified into two general types regarding physical form, e.g. the liquid and dry formulations. There are a number of varying types of formulations within each general classification. A description of these types and their general purposes follows.

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Liquid formulation types

Oil concentrates

Oil concentrates are liquid formulations containing, preferably, a high concentration of active ingredients. They are generally used after dilution to a practical or convenient low concentration with an inexpensive hydrocarbon solvent as fuel oil or diesel oil. The concentration may be expressed either in terms of weight of active ingredient per unit volume of concentrate or in terms of per cent by weight of active ingredient. It is necessary that the concentrate be miscible upon minimum agitation with the diluent to be used. Aromatic hydrocarbons such as xylene or heavy aromatic naphtha are generally used as solvents for the active ingredients in oil concentrates. There are pesticide chemicals whose solubility in these aromatics is so limited that they are impractical as solvents. To overcome this limitation, it is necessary to use a more powerful solvent, for example, isopropanol or cyclohexanone. The necesssary qualification for the use of any of these polar solvents is that the concentrate is miscible with the diluent oil which will be used.

Emulsifiable concentrates

Emulsifiable concentrates are similar to the oil concentrates with the exception that they contain a surfactant or emulsifier to permit the dilution of the concentrate with water for practical application. For best results, the solvent system must be immiscible with water. The most generally used solvents are the xylene type, the heavy aromatic naphtha type or, occasionally when the solubility of the pesticidal chemical is sufficient, aliphatics of the kerosene range.

Because of their convenience for the user, emulsifiable concentrates may be considered the most popular form in which pesticide formulations are used. They are expected to perform well under a wide variety of conditions and to withstand a number of extremes of packaging and storage. Although the ideal emulsifiable concentrate is frequently sought, it is seldom attained. It will be shown that either compromises must be made or other useful alternative formulation types accepted as being more practical for certain pesticidal chemicals. Functionally, emulsifiable concentrates must disperse spontaneously in waters of all hardness and with the aid of gentle agitation remain uniformly dispersed throughout the spraying period.

Aqueous concentrates

Aqueous concentrates are concentrates of pesticidal chemicals dissolved in water. The most frequently encountered pesticidal type found in this form is the salt of a herbicidal acid. Because the herbicidal acid is the nominal active ingredient, concentrations are generally expressed in terms of pounds of acid-equivalent per gallon. Since these active ingredients are soluble in water, there are generally no problems of miscibility, dispersability or suspendibility. The exception occurs when magnesium, calcium or iron of natural waters used for dilution may cause an insoluble precipitate; remedies do, however, exist for this situation.

Oil solutions

Oil solutions are ready-to-use formulations containing, generally, a low-odour, colourless solvent of the kerosene type and a pesticide chemical in low concentration. The concentration of active ingredient is usually under 5 per cent by weight. Oil solutions of insecticides are generally used for household or institutional insect control. In addition to low odour, these formulations must preferably be non-staining and have a high flash point to minimize the fire hazard.

Invert emulsifiable concentrates

Invert emulsifiable concentrates are distinguished from the normal emulsifiable concentrates by the fact that their dilution with water results in an emulsion in which the external or continuous phase of the emulsion is the oil portion, whereas the internal or discontinuous phase of the emulsion is water. These concentrates are used principally in the formulation of oil-soluble herbicidal esters. The solvent is usually an oil having relatively low vapour pressure. Field dilution is generally at a much lower ratio than that used for conventional emulsifiable concentrates and often less than ten parts of water to one part of concentrate by volume. The distinguishing feature of invert emulsions is that they form significantly larger droplets than conventional emulsifiable concentrates when emitted from special application equipment. Because the external phase contains an oil of relatively low vapour pressure, evaporation of the continuous phase is minimized. As a result, there is no reduction in the size of the droplet from the time it emerges from the application equipment until it impinges on the target. The probability of drift of the particle during its fall through the air is, therefore, greatly reduced.

Dry formulation types

The important dry formulation types are dust bases or dust concentrates, wettable powders, dusts, granules and pellets. All dry formulations with the exception of wettable powders are applied in the field in their dry form as dusts, granules or pellets. The dust bases or concentrates and wettable powders are intended for further dilution to field strength before final application. In the case of dust bases, locally available low-cost diluents such as clay and talc are usually mixed with the concentrate at a regional formulation plant. Wettable powders are generally mixed with water before field application and then applied as a spray. In general, the packaging of dry formulations is considered to be less of a problem than packaging of liquid formulations. The characteristic differences of the dry formulations follow.

Dust bases or concentrates

Dust bases or dust concentrates are dry, free-flowing powders containing a high concentration of active ingredients which varies generally from 25 to 75 per cent. Such products are seldom applied in this concentrated form. They are usually diluted or cut back to a practical concentration with a suitable inert material for final application in the field. Pesticide-fertilizer mixtures are often made by mixing the dust concentrate with the dry fertilizer. If granular fertilizers are being mixed with dust bases, a sticker is often necessary to prevent the segregation of the fine particles of the pesticide base which usually are below 200 mesh (74 μm) size.

Wettable powders

Wettable powders are similar to dust bases except that they are formulated for dilution with water into a final spray. The quality of wettable powders is judged by the rapidity of wetting when mixed with water and the suspendibility in water when mixed in practical dilutions for field application. The speed of wetting can be increased by the proper choice of wetting agents which reduce the interfacial tension between the particles and the water. Good suspendibility is attained by reducing the particle size, preferably to below 325 mesh (44 μm). Surfactants of the dispersant class are generally added to wettable powder as part of the regular formulation to prevent the agglomeration of particles and, in turn, decrease the rate of sedimentation, which is a function of particle size. Exceptionally fine particle size which further improves suspendibility is sometimes attained by air-milling the product to a particle size of 10 μm or less. Wettable powders are frequently used for the slurry treatment of seeds as well as in a variety of spraying techniques.

Dusts

Dusts are very finely powdered, dry pesticides. Dusts are formulated to field strength which may vary from 1 to 10 per cent active ingredient depending upon the potency of the pesticide and the rate of application. Dusts must be free-flowing so that they can be accurately metered in application equipment. Particle size may vary, although it is usually under 200 mesh (74 μm). For aerial application of dusts, the avoidance of drift is important; therefore, a moderate particle size and uniform distribution are necessary. Dust formulations applied by air or ground equipment are extremely advantageous when treating mature crops with dense foliage. This advantage is the inherent property of billowing around the foliage and covering the undersides of the leaves and the stems of the plant.

Granules

Granular pesticides are distinguished from powdered pesticides according to mesh size range. It is generally accepted that a granular pesticide is a product which is limited to a range from 4 mesh (United States standard sieve series) to 80 mesh. For any given material (for example, a product labelled 30/60), at least 90 per cent of the finished product must be within this specified mesh range, and the remaining 10 per cent may be distributed on either side of the specified mesh sizes. The presence of fines which may become airborne by a crosswind during application is generally considered to be objectionable in a granular product.

To be useful, granular pesticides must be non-caking during storage. To permit accurate application in metered application equipment, the granules must be free-flowing. Depending upon the field requirements, the granules may have fast or slow disintegration characteristics in the presence of moisture. The disintegration characteristics of granules after entering the soil have a direct bearing on the release rate of the pesticides.

The concentration of active ingredient in granular pesticides may vary from as little as 1 per cent to as high as 42 per cent depending upon the properties of the active ingredients, the characteristics of the carrier or upon other factors such as the potency of the insecticide and the desired rate of application of the finished product.

Pellets

Pesticide pellets are dry pesticide formulations in which the particle size is larger than that specified for granular pesticide, e.g. greater than 4 mesh. There are no established maximum sizes for pellets but, in practice, diameters may be as large as 0.6 cm and possibly 1.3 cm. Pellets are generally formed by mixing the active ingredient with a suitable inert ingredient plus a binder, if necessary. The mixing is followed by pan-granulating to the desired size or extruding (and crushing, as required) to the desired size. Concentrations of active ingredients may range from a fraction of a per cent as in the case of baits, in which an attractant, inert ingredient is used, to as high as 20 or 25 per cent, if fertilizer is added.

Other formulation types

A number of other possible formulation types are used for special purposes. These are better classified by themselves rather than with the familiar types because of their unique physical form or their unusual application. Both liquid and dry formulation types are encountered.

Aerosols

Since their development for insect control during the early years of the Second World War, aerosol insecticides have become a familiar form of pesticide formulation. As generally understood, aerosols are solutions of an active ingredient in a suitable solvent plus a propellant which is a gas dissolved in the insecticide solution and/or contained under pressure within the aerosol dispenser. The type of spray pattern and particle size of the spray are controlled by the design of the nozzle which is used and by the pressure in the container which forces the concentrate through the nozzle. The internal pressure is determined by the properties of the propellant gas. There are many different approaches to the formulation and packaging of an aerosol pesticide product including both non-aqueous and aqueous solvent systems.

Seed dressings

Seed dressings may be either a liquid or a dry type; indeed, there are variations within each type. Two of the most important requirements of a seed dressing are that the seed dressing must not interfere with the plantability of the seed; and that the seed dressing must not diminish the viability of the seed. In addition, it is most desirable (however, seldom attained) that the seed dressing is non-toxic and does not constitute an adulteration if the seed is later to be fed to livestock. Seed dressings must often contain a dye which colours the seed to indicate the chemical treatment. Certain seed dressings have been developed in dry concentrate form for the addition to seed grains in a planter box as controls of insects or diseases from the time of planting until after the seed has germinated. Wettable powder types of seed-treating formulations are used for the slurry treatment of feed as well as liquid types of certain emulsifiable concentrates and water-dispersible concentrates. The concentration of the active ingredient in seed-dressing formulations follows the same rules and limitations as other liquid and dry formulations.

Poison baits

Poison baits are special formulations designed to attract and kill certain types of foraging insects and rodents. Poison baits are designed to preferentially lure and poison these pests near or in their natural environment. They are frequently used as a barrier to intercept the migration of insects such as locusts into grain fields. In orchards, rodenticide baits are placed around the tree trunks to prevent their attack by rats. Another form of bait is used in the so-called bait trap for the control of Japanese beetles in orchards or gardens and for the control of the Mediterranean fruit fly in citrus groves. Rodenticide baits in pellet or meal form are widely used for municipal and residential rat control and for the control of mice and rats in farm buildings and grain storage areas.

Poison baits have numerous physical forms and composition. Where applicable, they have a distinct advantage in agricultural pest control by effectively reducing damage to agricultural crops by insects and rodents without the hazard of leaving a residue on the plant or crop to be protected.

Capsulated formulations

The encapsulation of pesticides is a relatively new development with the principal objective of providing a controlled release rate for specific types of pesticide action. An encapsulated pesticide is essentially a very small mass of a pesticidal composition surrounded by a continuous shell or envelope of a coating material. Two factors to be considered in the selection of the coating material are the material's chemical inertness toward the active ingredient and the material's ability to dissolve or disintegrate at a controlled rate by the action of certain environmental factors such as moisture or soil micro-organisms. Particle diameter varies from a few μm to 0.3 cm or larger. Theoretically, the concentration of the active ingredient contained in the shell wall varies from a fraction of 1 per cent up to and approaching a 100 per cent active ingredient. Although the shell thickness may be very small in comparison to the diameter, the percentage of the encapsulating shell material increases as the particle size decreases. Similarly, the cost of an encapsulated pesticide ingredient varies inversely with the per cent of concentration.

Fertilizer mixtures

The use of fertilizer mixtures containing an insecticide and/or herbicide has become standard practice in agriculture as well as in gardening. Although the use of pesticides with dry fertilizer mixtures has become generally acceptable, the use of pesticides emulsified or dispersed in liquid fertilizers has not attained acceptance. The concentration of pesticide in dry fertilizer mixtures is generally quite low and usually under 0.5 per cent. To meet field requirements in agricultural use, pesticide fertilizer mixtures are usually prepared by local fertilizer suppliers to order. Furthermore, because liquid fertilizers are usually applied by specialists, the special pesticide formulation must be added to a liquid fertilizer mixture prior to transportation to the field.

Pesticides are incorporated in dry fertilizers by spray impregnation or by blending of dust bases and granules. Because of the low concentration of pesticides in these products, great care must be exercised through efficient blending techniques to obtain a uniform product. Because of the trend towards the use of granular fertilizers, care must be taken in the formulation of these mixtures to prevent the possibility of segregation of the pesticide from the bulk of the fertilizer mixture. When using dust bases, it is often necessary to use a sticker to prevent segregation of the powdered insecticide. Granular pesticides should be roughly of the same size or mass as the fertilizer granules to avoid separation. When adding oil concentrates of pesticides to granular fertilizers, only a small quantity of liquid concentrate should be used to avoid a wet or sticky product that can wet and migrate through the walls of the shipping bags. The quantity of liquid varies with the density and porosity of the granule.

FUNCTIONAL PROPERTIES AND CHARACTERISTICS

The formulation of pesticides is a property-oriented technology. To the formulation chemist, the physical properties of the pesticidal chemicals are of greater concern than their chemical structure or their biological activities.

Active ingredients

The active ingredients are those portions of a formulation which possess biological properties. All other ingredients in the formulation are used to facilitate the application of the active ingredients to the desired target. For a given type of formulation, the physical properties of the active ingredients limit the choice of formulation ingredients.

Physical state

The physical state of a pesticidal chemical defines the form in which it occurs under normal ambient temperature conditions of shipping and storage. The physical state provides the first clue to the preferred method of handling the technical pesticidal chemical in the formulation process.

Pesticidal chemicals in their technical form may be encountered as liquids, fine crystals, powdered flakes, solid cakes or small lumps. The fine crystalline or powdered material is generally preferred when dust bases or wettable powders are to be made by dry-blending followed by grinding. For the preparation of liquid concentrates, any form of pesticide may be used. Heat is generally applied in dissolving solid pesticide for liquid formulations to increase the rate of solution. Because spray impregnation is the simplest and most effective way of preparing granular pesticides, the solid pesticidal chemicals are generally dissolved in a solvent to facilitate spraying. Some low melting solids, however, are heated sufficiently above the melting point and sprayed through heated lines and nozzles to obtain proper spray characteristics.

Some technical pesticidal chemicals in their normal state are waxy or semisolids and are most suitably packaged in thin-gauge metal containers or special leak-proof, lined or coated fibre drums. Pesticidal chemicals are removed from their containers by stripping away the container walls or by melting them and then pumping or pouring out the contents. Waxy or semisolid materials are processed by dissolving them in a suitable solvent with the aid of heat.

Melting or setting point

The melting point normally refers to the temperature at which a pure substance becomes a liquid. The setting point of a pesticidal chemical is the temperature at which a molten or liquid pesticide becomes a solid as a result of withdrawing heat from the system. The melting or setting point of a pesticidal chemical defines its physical state at room temperature.

The melting or setting point suggests the ease of grindability of the material; the grindability generally improves as the melting point of the pesticide increases. Materials with melting or setting points between 60° and 90° C can often be ground with the addition of dry sorbent carriers. However, care must be taken, especially with lower melting materials, to avoid a build-up of heat in the mill. Materials which melt below 60° C are more conveniently processed after melting or by dissolving in an appropriate solvent.

Boiling point

Most pesticidal chemicals have relatively high boiling points. In processing pesticide formulations, it is unlikely that temperatures will be encountered which approach the boiling point of the active ingredient.

Specific gravity or density

The specific gravity of a substance is a measure of the relative weight of a substance relative to the weight of an equal volume of water at the same temperature. Liquid and molten pesticides are pumped and metered into formulation equipment on a weight basis by applying the specific-gravity factors with temperature corrections. In this way, materials-handling and weighing problems can be greatly simplified. In the development of liquid formulations such as emulsifiable concentrations, the probable concentration of the active ingredient in the finished product can be reasonably estimated from the specific gravities of the active ingredients, solvent and surfactants.

In the design or preparation of liquid formulations such as emulsifiable concentrates, the volume of active ingredient and/or solute and the volume of solvent are not additive. Therefore, it is necessary to compute the volume of the active ingredient on the basis of its apparent solution density which has been shown in some cases to decrease with dilution.

Studies of the sorptivity of dry carriers and diluents indicate that the maximum quantity of liquid which can be held by a dry solid is a function of the volume of liquid rather than its weight. Therefore, when the volumetric sorptivity limits of a given carrier are known, the probable maximum weight percentage of the active ingredient which can be absorbed by the carrier can be estimated.

Viscosity

The viscosity of a pesticidal chemical is a functional characteristic which must be considered in all handling operations. Although viscosity is usually associated with liquid products, it is likewise an inherent characteristic of molten and solid chemicals. In the transference of technical pesticidal chemicals from their bulk containers into processing equipment, the power requirement at a given rate of flow increases as the viscosity increases. For pumping highly viscous materials, the use of a gear pump or a positive displacement pump (with a bypass) is preferred rather than the use of centrifugal pumps. This is especially true in cold weather when the temperature of the liquid may be relatively low.

In the spray impregnation of powdered or granular carriers for the preparation of dry formulations, a low viscosity is generally required for a good spray pattern. To reduce viscosity in the operation, it is necessary to warm the liquid to a suitable viscosity or to add a solvent which is miscible with the active ingredient. If heat is used to decrease the viscosity of the liquid being sprayed, the heat loss in the transfer lines from the spray kettle to the nozzle should be minimized by insulation so that the proper viscosity will be maintained throughout the entire spraying operation.

The viscosity of a pesticidal chemical is significant in emulsifiable concentrates; as the concentration of the active ingredient in emulsifiable concentrates increases, the viscosity increases. In general, the dispersibility of an emulsifiable concentrate in water improves as the viscosity of the concentrate decreases.

Solubility

The solubility of a pesticidal chemical is an inherent characteristic dependent upon its molecular structure and molecular weight. Although it is possible to set forth certain rules of solubility relating to molecular constitution, in practice it is necessary to experimentally determine the solubility characteristics of each new pesticidal chemical in representative solvents. In liquid concentrates, the solubility of pesticidal chemicals is usually expressed in terms of pounds of pesticidal chemical (active ingredient or total technical material) per gallon of solution Alternatively, in experimental work or where the metric system is used, solubility may be expressed in terms of grams of active ingredient or grams of technical pesticide/100 ml of solution. Other units such as weight of active ingredient or technical material per volume or per weight of solvent may be used, but practical application of these units requires additional calculation based upon density or apparent density.

The solubility of a pesticidal chemical is of high economic significance. It is normally desired that each pesticidal chemical has a very high degree of solubility, so that high concentrations can be prepared in low-cost solvents, such as kerosene. If the solubility is low, more expensive solvents may be required and even then only low concentrations may be attainable. If the cost of producing a liquid concentration becomes excessively high because of poor solubility properties, and if a spray-type formulation is required, alternative formulation types, such as wettable powders or flowable concentrates, should be considered.

Stability

The stability of a pesticidal chemical is its ability to withstand the degradative effects encountered in storage, formulation and the environment to which it is subjected after application. The principal concern is the stability of the molecule under all stresses rather than its stability under lowered temperatures or its persistence as a residue.

Although many organic molecules may decompose spontaneously during storage, this cannot be tolerated for a pesticidal chemical. If there is a tendency for decomposition, a stabilizer must often be added to the technical pesticide to significantly retard the tendency. Heat and the presence of impurities such as certain metallic substances or oxides may occasionally cause breakdown of pesticides. When this is the case, stabilizers are necessary or the impurities must be removed. During many formulation processes, the application of heat is often necessary to dissolve the pesticidal chemical or to reduce its viscosity. Therefore, the heat stability of the active ingredients must be studied. Regardless of the type of formulation to be made, the chemical compatibility of the formulation ingredients must be studied for prolonged periods of time. To accomplish this, it is necessary that sensitive and specific methods of analysis be developed prior to the initiation of the study (see chapter 5).

Some pesticidal chemicals are subject to decomposition in varying degrees by acids or bases. In formulation, this type of decomposition might be encountered with mineral carriers and diluents or, in certain cases, with the particular surfactants which are used. When working with pesticidal chemicals which are sensitive to strong acids or bases, care must be taken to avoid formulation ingredients with these properties. Other organic chemicals are very sensitive to hydrolysis by the action of water. If the rate of hydrolysis is too great or cannot be controlled, a serious limitation is placed upon this chemical for use in emulsifiable or any aqueous spray formulations. After application, the persistence of such a chemical is of such short duration that pest control is not provided. The ability of a pesticidal chemical to withstand degradation by air or light may be a factor to consider and the use of antioxidants or light-screening agents can be useful, although they are generally of only temporary utility.

Other properties

Two other characteristics of pesticidal chemicals are odour and colour. Although colour is of no importance in agricultural applications, odour and colour may be significant for household or institutional sprays. The avoidance of colour in spray formulations of insecticides may be accomplished in some cases by the removal of impurities through decolourizing processes in the technical product of the formulation. Where colour develops after formulation, a search is made for formulating ingredients which will not react with certain impurities in the technical material. Odour can sometimes be removed or greatly diminished by processing of the pesticidal chemical. However, it is generally more expedient to find a suitable aromatic masking agent to make the inherent odour of the formulation less obnoxious.

Powdered carriers and diluents

The most important dry carriers and diluents used in pesticide formulations are inorganic materials principally of natural origin (see table 1). They include minerals such as diatomite, vermiculite, attapulgite, montmorillonite, talc, pyrophyllite and kaolinite. They are processed for use in pesticide formulations by many techniques ranging from simple drying and pulverizing to washing, air-floating and calcining. Their properties are imparted by the crystalline and molecular structures as well as by the composition. The properties of these carriers and diluents are often enhanced by unique processing conditions. The properties of powdered carriers and diluents are now described.

Particle size

The powdered carriers and diluents are distinguished from the granular carriers and diluents principally on the basis of particle size. Most pesticidal carriers and diluents are finer than 200 mesh (United States standard sieve series). In general, dry carriers and diluents are used for the formulation of dusts, dust bases and wettable powders. Generally, the finer the particle size, the more suitable the material will be for wettable powder formulations because the suspendibility in water of a wettable powder is inversely proportional to the particle size. For this type of product, a minimum of 95 per cent of the carrier or diluent should pass through a 325 mesh (44 μm) screen.

Sorptivity

Relative sorptivity is the usual measure for distinguishing between dry carriers and diluents. Sorptive carriers are necessary when liquid or low melting pesticidal chemicals or solutions are to be formulated as dust bases or wettable powder concentrates. For the formulation of dusting powders of pesticides, sorptivity is of minor significance for all practical purposes.

Sorptivity may be defined as the capacity of a powdered inert material to maintain the addition of a liquid in a quantity up to but not exceeding the transition point between dryness and plasticity of the total mass. One laboratory has adopted the term "sorption index" as the weight of technical material which can be absorbed by 100 g of the inert powdered mineral up to the point of plasticity as defined above (see table 1). The method for determining the sorption index is similar to the method used in the paint industry for determining the oil absorption value of pigments.

In practice, the quantity of liquid pesticide added to a carrier never approaches the quantity which is designated by the sorption index, for to do so would very likely produce a highly non-flowable mixture. For example, diatomaceous earth which has a sorption index of around 270 may be used with care to produce

TABLE 1. GENERAL PHYSICAL PROPERTIES OF CARRIERS AND DILUENTS

Carrier or diluent	*Specific gravity*	*Loose pack density (lb/ft³)*	*Packed density (lb/ft³)*	*Oil sorptivity (g/100 g)*	*Sorption index*
Attapulgite	2.3/2.4	16/25	29/36	100	135/237
Calcium carbonate	2.7	40/55	80/96	5/18	. . .
Diatomaceous earth	1.8/2.1	6/10	10/17	100/220	187/272
Kaolinite	2.4/2.7	15/17	38/80	5/54	69/184
Mica and vermiculite (expanded)	2.2/2.7	8/46	10/46	38	. . .
Montmorillonite	2.3/2.8	16/54	18/64	23/70	80
Pumice	2.6	30	45/48	. . .	78
Pyrophyllite	2.6/2.8	28/35	52/62	25/50	76/90
Silica	1.9/2.7	3/40	25/40	26/09	64
Talc	2.6/2.9	28/46	28/63	24/40	73

Carrier or diluent	*Maximum flowable concentrate (per cent)*					*pH*	*pK*	*Approximate deactivation required for pK 1.5*
	Heptachlor	*Chlordane*	*Endrin*	*Methyl parathion*	*Ethyl parathion*			
Attapulgite	25	40/50	75	25	25	5.2/8.0	<1	6—10
Calcium carbonate	5	5	75	5	5	9.0/9.2	>3.3	0
Diatomaceous earth	50	70	75	50	60	5.5/7.0	1	1—5
Kaolinite	. . .	20/40	75	10/15	15	4.2/9.4	<1	0—3
Mica and vermiculite (expanded)	25/40	55/60	75	. . .	. . .	6.9/7.1	. . .	1—3
Montmorillonite	5/25	5/40	75	5/25	5/40	4.5/9.4	<1	4—>9
Perlite	25	40	75	25	40	. . .	. . .	0
Pumice	15/20	20/25	75	15/20	20/25	5.4/8.1	. . .	0—1
Pyrophyllite	5/10	5/10	75	5/10	5/10	6.0/7.0	3.3	0—1
Silica	5/60	5/75	75	5/60	5/75	4 5/10.0	. . .	0—10
Talc	5/10	5/10	75	5/10	5/10	6.8/9.6	3.3	0—1

a chlordane 50 per cent dust base. (The dust base consists of 50 per cent technical chlordane and 50 per cent diatomaceous earth.) If this 50 per cent concentration of chlordane is exceeded, the product becomes increasingly heavier and less flowable, which makes it more difficult to dilute with an inert diluent. It is often necessary to add other ingredients such as solvents, liquid deactivators and surfactants; all these additional ingredients have a great tendency to reduce the available sorptivity of the inert carrier portion.

Table 2 lists a number of typical carriers and diluents according to their sorption index. It shows that synthetic silica, diatomite and attapulgite have high sorption indices, whereas pyrophyllite, talc and powdered limestone (calcium carbonate) have very low sorption indices and are, therefore, classified as diluents.

TABLE 2. SORPTIVITY OF MINERAL TYPES COMMONLY USED AS PESTICIDE CARRIERS AND DILUENTS

Mineral	*Typical sorption index*[a]
Carrier	
Silica (synthetic)	400
Diatomite (salt water)	270
Vermiculite (expanded)	250
Attapulgite	230
Diatomite (fresh water)	200
Perlite	200
Montmorillonite (non-bentonoid)	190
Kaolinite	160
Diluent	
Pyrophyllite	90
Bentonite	80
Pumice	78
Talc	73
Silica (natural)	64
Limestone ($CaCO_3$)	50
Gypsum ($CaSO_4$)	50

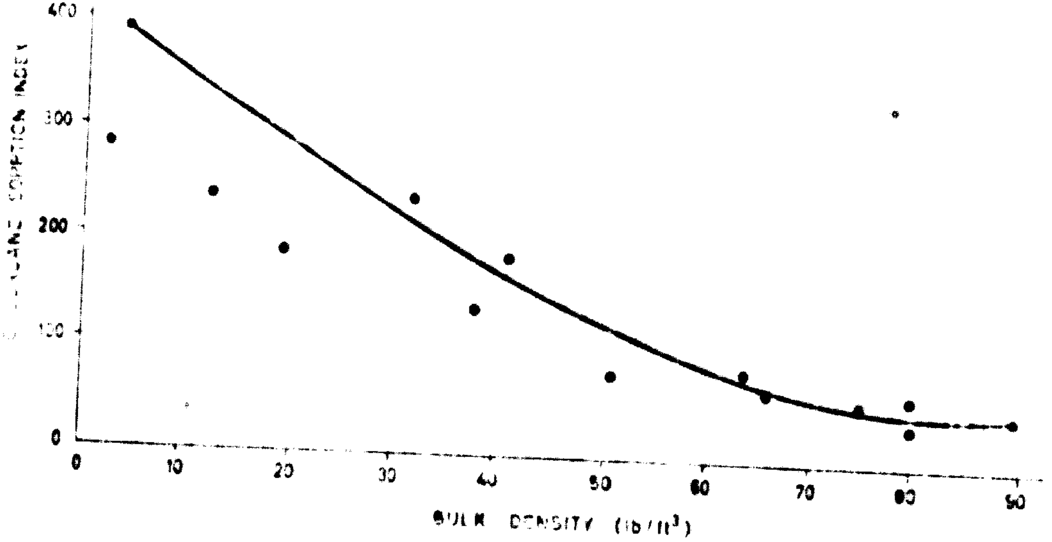
[a] The quantity of chlordane absorbed in the rub-out method (g/100 g of powdered material).

If the sorptivity of a carrier is determined as mentioned above by using liquids of varying densities, it will be found that the sorptive capacity in terms of the weight material absorbed varies inversely as the density of the liquid. The linseed oil absorption of many minerals used as carriers and diluents is frequently given by the suppliers. If the linseed oil absorption value is known, the chlordane absorption or sorption index, for example, can be estimated through multiplication by the ratio of the higher to the lower density.

Bulk density

Bulk density generally varies inversely as the sorptivity of the carrier or diluent. Therefore, diluents tend to be heavier than carriers. This is illustrated in figure 1, where bulk density in lb/ft³ for a random selection of carriers is plotted versus the chlordane sorption index. The bulk density of carriers and diluents can be measured by two different techniques.

Figure 1. Sorption index as a function of bulk density



The loose packed (or aerated) bulk density technique gives the bulk density in its fluffed-up form as determined with the Scott volumeter. This is a measurement of randomly oriented particles that are allowed to fall a minimum distance and to settle without orientation. It is a useful index in estimating the maximum amount of carrier or diluent which might be added to a dry blender. When a blender is in operation, the powdered material which it contains is continually being circulated so that aeration and disorientation are at a maximum.

The packed bulk density technique gives the weight of a volume of powdered material after it has been vibrated to maximum orientation. The material has been completely deaerated and the particles are permitted to settle in their most stable geometric alignment. Packed bulk density is the index of the greatest weight of the powdered material which can be packed in a container of any given size (see table 1). The ratio between the loose packed density and the packed bulk or vibrated density varies from material to material according to specific gravity, particle shape and particle size distribution.

Surface acidity and chemical compatibility

Surface acidity is a common characteristic of most naturally occurring mineral carriers and diluents but varies in degree depending upon the crystalline and molecular structures of the mineral. Surface acidity may be defined as a disproportionate distribution of electric charges in the mineral to produce a surface with positively charged centres. These centres are referred to as acid sites or electrophilic centres. The strength of these positively charged sites can vary depending upon the composition of the surface and the degree of distortion in the structure which brings about the disproportionate distribution of the electrical surface charges.

The acidity will, in turn, affect reactions with other chemicals. The strength of the acid centres may be measured by certain sensitive dyestuffs known as Hammett indicators which change colour at very specific acid strengths. These dyes form conjugated bases with the nucleophilic acid centres at different surface acidities which are defined as the pK with a numerical system ranging from +7 to −8. Consequently, the pK is a measure of acid strength (i.e. the affinity for electrons) of the average acid site.

In practice, the strength of the acid site is of importance as well as the number of acid sites in a given mass or weight of the mineral. For example, the most active acid sites of kaolinite probably have a pK equal to −8; kaolinite has only about one-third as many acid sites as montmorillonite for a given weight of material. The surface acidity of a mineral carrier or diluent is of great importance for the stability or rate of decomposition of the active ingredient in the finished formulation.

Pesticidal chemicals vary greatly in their susceptibility to decomposition as the result of the "catalytic" activity of the acid sites. Fortunately, these acid sites can be deactivated with certain organic chemicals which preferentially share their electrons with the mineral to form a covalent bond which is stronger than bonds formed between the pesticidal chemical and the acid centre itself. Compounds containing oxygen in an ether linkage or amine derivatives are effective for this use.

For surface active minerals, deactivators should be tested for compatibility with the pesticidal ingredients in the entire system. Although urea and hexamethylenetetramine are excellent deactivators for formulating some materials such as aldrin and endrin, respectively, they are not suitable for use in heptachlor formulations where a different decomposition mechanism is encountered. For heptachlor and chlordane, diethylene glycol and similar neutral substances perform well as deactivators without encountering any degradative reaction with the active ingredient.[1] Usually 6 or 8 per cent of the deactivator material is added. Its use increases the cost of formulation. When other properties and characteristics of the carrier and diluent are satisfactory for a given formulation, an inert material with the least surface acidity should be selected.

The acidity or alkalinity of carriers and diluents may cause the decomposition of certain pesticides. Consequently, only those inert ingredients which in accelerated storage tests do not affect the active ingredient should be considered in the formulation. The acidity inferred here is the more classical acidity and not surface acidity discussed above. This acidity can be determined by measuring the pH of a 10 per cent slurry of the mineral in water.

Furthermore, the presence of metallic impurities such as iron oxides in certain clays can have a deleterious effect upon the active ingredient. If the pesticidal chemical is sensitive to metallic impurities, materials should be selected which do not contain extractable iron salts.[2]

Flowability

The flowability of a powdered carrier is the ease with which the material can be poured, moved or displaced; it is dependent upon particle shape, density

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[1] **Malina, M. A.** *et al.* (1956) *Journal of Agricultural and Food Chemistry*, Vol. 4, p. 1038.

[2] **Holler, H. L.** *et al.* (1945) *Industrial & Engineering Chemistry*, Vol. 37, p. 403.

and to a lesser extent, particle size. Its significance in the formulation process is that as flowability increases, the power requirement for blending or working the material decreases. This is a significant factor in field application because, as flowability increases, the flow through the dusting hopper and the meter improves, and the rate is more easily controlled.

Dustability

Dustability is a characteristic of powdered diluents relating to the ability to flow through the air, to be transported by air currents within a limited area of application and to cling to the surface of the crop after application. There are no precise laboratory methods for testing the dustability other than practical application under actual or simulated conditions of use.

Abrasiveness

Abrasiveness is the property of certain carriers and diluents to cause wear of processing equipment, metering devices and orifices of application equipment. Wettable powders prepared from abrasive carriers and diluted in water can cause the continued enlargement of fine orifices of spray nozzles through the abrasive process. This action significantly changes the flow characteristics of the nozzles thereby increasing spray volume rates. The spray pattern is changed and the resulting applications are inaccurate. Abrasive materials include pyrophyllite, pumice, silica and diatomite, while non-abrasive materials include kaolinite and talc.

Granular carriers

Granular carriers are particulate materials which form the basis for most granular pesticides. These carriers may be of mineral or vegetable origin, but clays such as attapulgite and montmorillonite are predominantly used as granular carriers. Because granular pesticides are most conveniently prepared by impregnating the granular carrier with the pesticidal chemical, sorptivity is a desirable property.

Particle size

An unofficial designation of a granular carrier is that it must have a particle size lying within the range of 4 mesh to 80 mesh (4 mesh is approximately 4,460 μm; 80 mesh is 177 μm). In practice, this broad particle size range is not used. Much narrower ranges are conventionally used for purposes of product uniformity, minimum segregation, accurate metering and optimum particle distribution. These size ranges may be of the following designations: 8/15, 16/30, 20/35, 20/40 and 30/60. A number of suppliers of granular carriers have adopted the standard that at least 90 per cent of all particles in a given designation shall fall within the stated mesh range. As an example, the designation 16/30 states that 90 per cent of the particles should lie within the range of 16 and 30 mesh, and that the remaining 10 per cent may be distributed on the 16 mesh screen and through the 30 mesh screen.

TABLE 3. VARIATION IN DISTRIBUTION OF PARTICLES IN A GIVEN MESH RANGE OF TWO CARRIERS

Designation	*Carrier (%)*	
	A	*B*
20/25	10	20
25/30	30	40
30/35	40	30
35/40	20	10

A 16-mesh screen has a size designation of 1,190 μm whereas a 30-mesh screen is equivalent to a 590 μm opening. The 16/30 designation, however, does not define the distribution of the particles in this range. Indeed, the majority of particles can be in the 18 to 20 mesh range for one product and in the 20 to 25 mesh range for another product. Yet, both products would meet the 16/30 designation or specification as indicated in table 3. Where the finer particle size distribution is encountered and the distribution is skewed toward the 25 or 30 mesh designation, there will be more particle/lb than if the skewness is in the opposite direction or towards the larger particle size. Table 4 illustrates the mesh size and particle/lb ratio. It may be argued that better distribution in application may be obtained by a granular product having skewness toward the finer mesh range. However, there is no evidence of practical benefit. Field research has shown that this factor is of little significance. The number of particle/lb of a granular product is dependent upon the particle size, distribution of particle size and the bulk density of the granular carrier.

TABLE 4. THE RELATIONSHIP BETWEEN MESH SIZE AND PARTICLES PER POUND OF FLOREX ATTAPULGITE GRANULES

Mesh size	*Particle/lb*
16/30	1,210,000
18/35	2,330,000
25/50	9,200,000
30/60	11,250,000

Sorptivity

The sorptivity of granular carriers has the same functional purpose as the sorptivity of powdered carriers. It is a function of both the crystalline structure and the available surface area of the material. For granular carriers of minerals such as attapulgite and montmorillonite which have a relatively high pore density, the sorptivity approaches that of the respective powdered carriers. Granular pyrophyllite and granular limestone have relatively low pore density so that sorptivity is principally a surface phenomenon. As particle size increases, surface area decreases; therefore, for the latter class of granular carriers, sorptive capacity is relatively low.

Attapulgite is often extruded in the process of manufacturing granules to improve sorptivity. The extruded granules are then calcined, thus affecting the moisture content, catalytic activity, hardness and tendency of the granules to break down in water. The following designations are used to identify the type and degree of processing:

A — unextruded;
AA — extruded;
RVM — (regular volatile matter)
uncalcined, rapid water break-down;
LVM — (low volatile matter)
calcined, resists disintegration in water.

Granular vermiculite is a laminar mineral which can be expanded by heat to produce a sorptive material. Its sorptive properties are caused by the capillary spaces between the layers. The general acceptance of granular vermiculite as a carrier has been limited, however, by its low bulk density.

Granular materials of vegetable origin include maize cob grits and ground walnut or pecan shells. The sorptivity of maize cob grits approaches that of the attapulgite or montmorillonite granules. The sorptivity of maize cob grits varies with the source and the process used. Walnut and pecan shells have less than half the sorptivity of the attapulgite granules.

Bulk density

The bulk density of granular carriers is a weight-limiting factor for a granular pesticide which is loaded into the hopper of the application equipment. Because sorptivity varies inversely as the bulk density, a lower weight of the sorptive granules can be loaded into the hopper of application equipment than the same volume of heavier but less sorptive granules. For practical purposes, attapulgite granules are acceptable on the basis of both bulk density and sorptivity. The process of impregnating attapulgite granules with liquid pesticides or liquid pesticide solutions does not change the shape or the size of the particle. During the impregnation process, the liquids are absorbed by the particle structure so that the weight of the particles increases without a significant change in volume.

Granular application flow rates are controlled by volumetric metering through adjustable and calibrated orifices in the application equipment. Therefore, it is necessary that the bulk density of the finished product be controlled. In addition to the effect on bulk density (assuming no attrition of the particles), as the weight of solvent increases and the weight of the granular carrier decreases, the number of particles per pound of finished product decreases likewise.

Surface acidity

The mineral types used for granular carriers are the same as those used for powdered carriers and diluents. Consequently, they have the same type of surface acidity and must be treated accordingly.

Mechanical strength

The mechanical strength of a granular carrier is its resistance to attrition under mechanical stress during the formulation process, packaging, shipment and use. When attrition does occur, the granules undergo a reduction in particle size with the generation of undesirable fines. Montmorillonite and attapulgite (especially the RVM grades) generally have satisfactory mechanical strength. Materials of vegetable origin, such as maize cob grits and pecan and walnut shell granules, are resistant to attrition.

Water break-down

The release of the active ingredient from most granular pesticides is made possible by the disintegration of the granular particles by the action of water. Granular clays such as attapulgite and montmorillonite (especially of the bentonite type) have the property of breaking down or swelling as a result of hydration. This phenomenon makes possible the release of the active ingredient. Pyrophyllite and calcium carbonate do not behave in such a manner.

Solvents

Because most pesticidal chemicals are insoluble in water, it is necessary to use some form of organic solvent for the preparation of liquid formulations or liquid concentrates used for the impregnation of dry formulations. The different types of solvents for pesticide formulations are classified by composition, chemical type, structure or function. In pesticide formulation work, it is convenient to classify the solvents as polar or non-polar. Among the non-polar solvents, the most important economically are the hydrocarbon and petroleum distillate solvents. The polar solvents include ketones, esters, glycols, glycol ethers and acid amides. The hydrocarbon and petroleum distillates are further classified as aliphatic or aromatic types for a functional, as well as an economic, distinction.

The formulation chemist may encounter water-miscible and water-immiscible types among the polar solvents. Although there may be a broad choice of available polar solvents, the question of water miscibility, together with other factors including economics, will influence the choice. The important functional properties of the solvents used in formulating pesticides are discussed below.

Distillation range and boiling point

The distillation range or boiling point of a solvent is an indication of the volatility of the solvent under formulation or application conditions. For pure solvents, the boiling point is the temperature at a given pressure where the liquid phase is in equilibrium with the vapour phase of the material. The normal boiling point usually refers to the temperature measured at atmospheric pressure.

The hydrocarbon solvents and petroleum distillates normally used in pesticide formulation are mixtures of hydrocarbons that each has its own boiling point. To determine the boiling-point range, it is convenient to distill the material and record the temperatures from the initial drop received in the overhead and through fractional points as volume per cent, until no further material from the sample is distilled (this is sometimes known as the Engler distillation). Typical hydrocarbon solvents used in pesticide formulation are the xylene type solvents which distill over a range from approximately 133° to 165° C. The heavy aromatic naphthas normally distill in the range from 117° C to approximately 287° C. Aliphatic hydrocarbon solvents are used in large quantities; they are principally of the kerosene type and distill in the range from 190° C to approximately 475° C.

Polar solvents are usually of relatively high purity as compared to the hydrocarbon solvents, and their distillation range is seldom greater than 12° C. In selecting a polar solvent, those with boiling points higher than the range from 94° to 99° C are preferred. In special cases involving solubility or phytotoxicity, materials with lower boiling points may be used with caution.

Specific gravity (density)

The specific gravity of a solvent is the weight of a given volume of the solvent relative to the weight of an equal volume of water at a standard temperature. Thus, when the specific gravity of the solvent is multiplied by 8.34 (equal to the weight in pounds of 1 gallon of water), the weight in pounds of 1 gallon of solvent is obtained. The density of the solvent is usually expressed in units of grams per millilitre (g/ml). When defining the temperature at which the density was determined, the density becomes an absolute value. Of the hydrocarbon solvents used in pesticide formulation, the aliphatic types such as kerosene have the lowest density values that range from 0.76 to 0.79. The xylene types have intermediate density values in the range from 0.85 to 0.88. The density of heavy aromatic naphthas range from 0.92 to 0.97.

Kauri-butanol value

The kauri-butanol value (sometimes called the KB) is a measure of the solvency of a given solvent. It is a relative number compared to that of toluene (= 105). For most aromatic hydrocarbons used in pesticide formulation, the KB value is nearly equivalent to the volume per cent of aromatics available in the solvent.

Aromatics content

The aromatics content of a hydrocarbon solvent such as those used in pesticide formulation is measured in terms of volume per cent. As a general rule, the solvency power of the solvent increases as the aromatics content increases. The cost of the solvent increases as the aromatics content and solvency increase. The aromatics content of xylene type solvents and heavy aromatic naphthas range from 85 to more than 95 per cent.

Specification sheets for solvents furnished by suppliers usually include inspection data for a typical batch or lot of a solvent. Occasionally, the typical aromatics content of a solvent will be listed as around 95 per cent with a specification given as minimum 90 or 91 per cent. When developing emulsifiable or oil concentrates with pesticides having limited solubility at low temperatures, the formulation chemist should perform cold stability tests using samples of solvents having KB values and per cent aromatics as close as possible to the lower limit of the specification for a particular solvent.

Flash point

The flash point of a solvent is an indication of the flammability of that solvent. Numerically, it is the temperature of ignition when tested under closely prescribed conditions using standard test apparatus. In selecting a solvent for pesticide formulation, a solvent should be chosen with the highest flash point consistent with other desirable properties. For most liquid formulations, the minimum flash point should be 27° C. Any liquids determined by the Tag Open Cup flash point method[3] as having a flash point below this temperature should be packaged in a container carrying a Bureau of Explosives red caution label for flammable liquids as prescribed in the regulations of United States Department of Transportation (USDT). If solvents having a lower flash point are used, extra precautionary measures must be used to avoid fire hazards during both formulation and shipping.

Solvency

Solvency is the ability of a given solvent to dissolve a specific material or class of materials when tested under prescribed conditions. The solvency of solvents used in pesticide formulations usually increases in the order of aliphatics, aromatics to polar compounds. Even though this is a broad generalization, it is reliable for formulation chemists and permits a few tests of new pesticidal chemicals with the minimum number of test solvents of each class.

The solvency requirements for the different classes of pesticidal chemicals vary considerably. Indeed, even within a given class of pesticides, such as the diene chlorinated hydrocarbons, there is a wide range of solvency demand. For example, any ordinary kerosene, which is one of the poorer solvents, will dissolve an infinite weight of technical chlordane. However, endrin has a very limited solubility in the aromatics and is seldom formulated at concentrations higher than 20 per cent by weight or 1.6 lb/gal.

Solubility may be expressed in a number of units such as the weight of the solute in grams per 100 g of solvent, the per cent by weight of the solute in grams per 100 g of solution and the weight of the solute in grams per 100 ml of solution. Solvency tests cover a range of temperatures usually extending to —16° C. Where extreme cold weather conditions are encountered, cold-stability tests are sometimes performed at temperatures as low as —39° C.

Water miscibility

In preparing emulsifiable concentrates, it is important to choose solvents which are relatively insoluble in water. The aliphatic and aromatic hydrocarbon solvents meet this requirement; however, the problem becomes more acute when the polarity of the solvents is increased, since it is usually accompanied by increasing solubility in water. Although solvents such as cyclohexane and isophorone are slightly soluble in water, they can often be used effectively, particularly when combined with aromatic hydrocarbons. Solvents of increasing polarity such as glycol ethers and amide solvents may be used usually only sparingly in mixtures with hydrocarbon solvents.

Viscosity

The viscosity has a minor, yet real effect upon the quality or characteristics of an emulsifiable concentrate. As the viscosity of a solvent used in an emulsifiable

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[3] Jacobs, M. B. and L. Scheflan (1953) *Chemical Analysis of Industrial Solvents*, Interscience Publishers, New York, pp. 109—111.

concentrate increases, the rate of crystallization decreases when the temperature of the concentrate drops below the solution saturation point. Therefore, caution must be exercised during cold-stability studies performed during a minimum period of time to avoid determining solubility at a given low temperature when, in fact, the formation of crystals in the concentrate is only delayed. A high viscosity apparently retards the molecular and crystal alignment. Seeding (the addition of a very small quantity of the crystalline material to the solution) may sometimes accelerate the rate of crystallization by providing nucleating surfaces for further crystal growth from the supersaturated solution.

The ease of dispersibility in water of an emulsifiable concentrate is inversely proportional to the viscosity of the concentrate. Therefore, non-viscous concentrates are best prepared with a solvent having as low a viscosity as possible while maintaining the most desirable solubility characteristics.

Toxicity

It is necessary in formulating pesticides to avoid human injury from chemical application to crops and plants. The hydrocarbon solvents are generally more phytotoxic than other solvent types. The higher boiling hydrocarbons are more phytotoxic than the lighter solvents.

Colour

The colour of a solvent has no practical significance when it is used for agricultural formulations. For household and institutional pesticide formulations, however, the colour of a solvent may stain walls and furniture. Therefore, if the formulation is to be used in the home or in other areas where staining of the applied surfaces is objectionable, the solvent should either be colourless or very light in colour. Most of the petroleum companies, which supply aliphatic solvents, provide special kerosene-type, so-called odourless and colourless insecticide base oils especially for the pesticide industry.

Odour

The odour of a solvent used for agricultural formulations is of minor significance; however, most hydrocarbon solvents have a characteristic odour. Gross changes in the odour of a solvent may be due to a change in composition and should be checked for possible effect on phytotoxicity as well as on the solvency of the material.

The odour of a household or institutional formulation must be kept to a minimum to avoid consumer sensitivities. The aliphatic solvents marketed as odourless insecticide base oils are generally satisfactory in this regard. Occasionally, special fragrances or masking agents are added to the formulation for a more pleasing odour. Most of the major essential oil and perfume supply houses have developed products especially for this use.

Surfactants

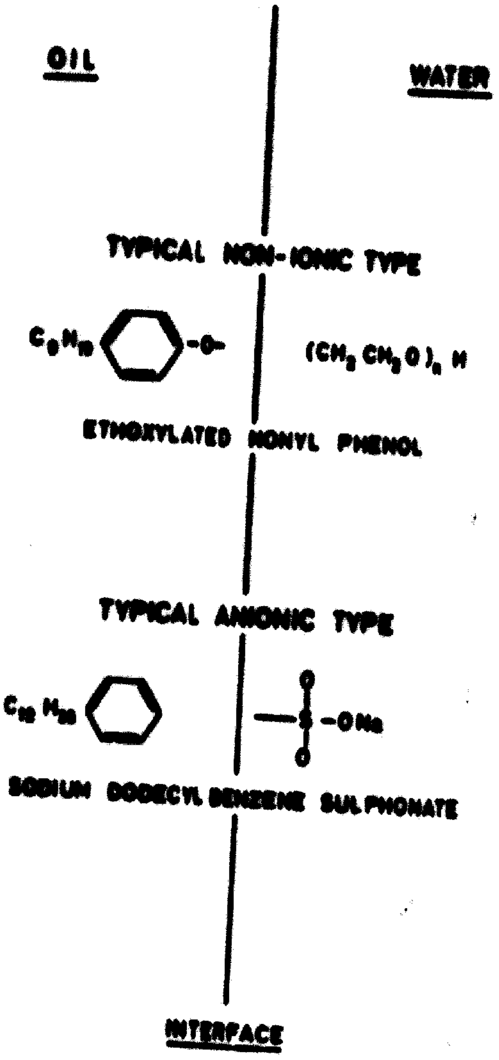
Surfactants reduce the interfacial tension between immiscible liquids or between liquids and solid surfaces. There are a number of functional classifications depending upon the predominantly surfactant characteristics. In pesticide formulation the surfactant characteristics of greatest interest are wetting and dispersing for wettable powders and emulsifying for emulsifiable concentrates.

A surfactant is used for the management of systems containing two immiscible phases. The molecular structure of a surfactant, therefore, should consist of one portion oriented toward one phase, while the other portion of the molecule is oriented toward the second phase of the system. If the system is oil and water, one portion of the molecule should be soluble in oil and the other in water.

Chemical types of surfactants

Surfactant molecules are anionic, non-ionic and cationic chemical types. In formulating agricultural pesticides, the anionic and non-ionic surfactants are the most important. Figure 2 shows the schematic function of these two surfactants. Although the cationics hold theoretical interest, they have not been used practically to any significant degree. A fourth type is the amphoteric surfactant that combines the properties of the anionic and cationic surfactants and functions as

Figure 2. Schematic function of surfactant molecules



either type depending upon the pH of the total emulsion. The non-ionic emulsifiers are compatible with either anionic or cationic emulsifiers. Cationic emulsifiers and anionic emulsifiers are, however, incompatible with each other.

The wetting agents used in wettable powders are usually of the anionic type; of these the largest number are probably the sodium salts of alkyl benzene sulphonates. Dispersing agents used in wettable powders function by imparting the same electrical charge to all particles in suspension. The effect is that the individual particles repel each other and, consequently, resist flocculation and agglomeration. Dispersants used in the formulation of wettable powder pesticides may be of the lignosulphonate type with cations such as sodium or calcium or the sodium or calcium sulphonates of polymeric phenols. Dispersants are generally dry, powdered solids which facilitate their incorporation in wettable powders.

Solubility and miscibility

In order that a pesticide emulsifiable concentrate be a completely homogeneous liquid, all components must be soluble in each other in the complete system under all conditions of storage and testing. In the development of an emulsifiable concentrate, the first step is to find a suitable solvent for the toxicant which is to be formulated. Then the emulsifier is selected which gives the best dispersibility and emulsion performance. Subsequently, storage tests are performed to establish the solubility and compatibility of the emulsifier with the toxicant-solvent system. Normally, and especially when aromatic type solvents are used, surfactant systems will remain miscible in the formulation. However, when the solvent is aliphatic, such as kerosene, and the concentration of the active ingredient is relatively low, such as 20 per cent chlordane, the emulsifier system may separate from the concentrate. This separation can be avoided by working with emulsifier systems which are soluble in or miscible with kerosene or by partial or complete substitution of the kerosene with a xylene or other aromatic solvent.

Compatibility

In selecting an emulsifier for an emulsifiable concentrate, tests must be performed to verify that a chemical reaction is not taking place between the emulsifier and the active ingredient. Such degradative action may result in a loss of toxicant strength in the formulations as well as a loss in the emulsifiability of the system. Special caution should be taken in the use of emulsifiers containing amine salts of anionic emulsifiers which may react with certain chlorinated hydrocarbons or with phosphate-ester active ingredients. A clue to this type of interaction may be shown by a rapid darkening of the system. Furthermore, the interaction is found by assays and emulsifiability tests after accelerated storage tests.

Stability

The anionic and the ether-type non-ionic emulsifiers used in pesticide formulations are for all practical purposes stable. On the other hand, ester-type non-ionic surfactants may decompose under long-term or accelerated storage conditions. The presence of free hydrogen chloride from the dehydrochlorination of certain chlorinated hydrocarbon pesticides may cause a hydrolysis of the ester linkage. The cationic surfactants or emulsifiers used in pesticide formulations are for all practical purposes stable.

Physical state

The surfactants used in pesticide formulation are solids or liquids. There are no known volatile surfactants for the formulation of emulsifiable concentrates. For their formulation, liquid surfactants are the most convenient. They can be easily pumped or metered into the mixing tanks and blended with normal agitation.

For wettable powder formulations, solid or dry wetting agents and dispersants are preferred. For the most efficient mixing by a dry blender, the particle size should be reasonably small (less than 100 mesh) to facilitate uniform blending.

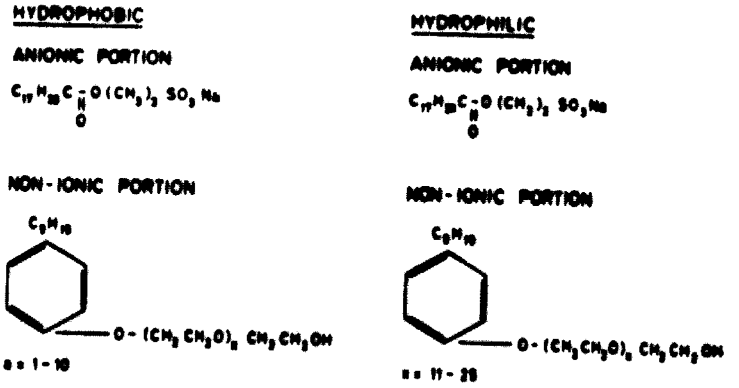
Some liquid emulsifiers used in pesticide formulation may show partial crystallization after lengthy storage. When crystallization occurs in packing drums, it is advisable to warm the drum and to mix the contents by rolling or tumbling the drum before it is emptied. This technique will ensure a uniform composition of the contents. To avoid normal crystallization, some emulsifier manufacturers add a small quantity of solvent to maintain a homogeneous liquid product.

Paired emulsifiers

The very large number of different molecular structures and compositions of pesticidal compounds causes large variations in emulsifiability. Furthermore, the varying solubility of pesticidal chemicals in different solvents is another complex factor in the selection of the proper emulsifier for a system. A further complication is that the final concentrate must perform equally well in water of varying hardness ranging from very soft to very hard. Indeed, even the temperature of the water which is used for the dilution of the concentrate in the field may have an important effect on the emulsifiability.

As the number of pesticide formulations and different products demanded for field use increased, the logistics of maintaining a specific emulsifier or emulsifier blends for each new product became unmanageable. This was particularly apparent in purchasing, inventory control and warehousing. To meet the need for simplification in emulsifier selection, manufactuers developed paired-emulsifier systems. Figure 3 illustrates one of these systems. The paired-emulsifier system consists of two products; each is based on a blend of anionic and non-ionic emulsifiers with different hydrophilic and lipophilic characteristics (i.e. one member of the pair will have emulsifying characteristics suitable for pesticide-solvent blends which are lipophilic in nature, and the characteristics of the other member will favour the emulsification of the hydrophilic pesticide-solvent system). These systems can be used for 90 to 95 per cent or more of the formulation requirements by simple determinations of the proper ratio and quantity which should be blended with the solvent-pesticide mixture to be emulsified.

Figure 3. A paired emulsifier system



Because of variations from lot to lot of solvent or from batch to batch of the pesticidal chemical, adjustments may be required in the hydrophile-lipophile balance of the emulsifier system in order to obtain uniform emulsification in the finished product. The adjustments are greatly implemented by the use of the paired-emulsifier system. When satisfactory performance cannot be obtained with the existing paired-emulsifier system or with either one of the pair separately, the manufacturer supplies a supplementary emulsifier, which is usually required on the hydrophilic side of the hydrophile-lipophile balance. This supplementary emulsifier together with the paired-emulsifier system extends the versatility of the paired-emulsifier concept.

Adjuvants

Adjuvants are added to pesticidal formulations to improve quality or performance characteristics. Because the objectives of the pesticide formulations are optimum effectiveness, safety to desirable crops and ease of application, adjuvants may be of different types and perform different functions. A few of the more important types, their usage and available materials for these uses are described below.

Deactivators

Many of the clays, minerals and inorganic substances used as carriers and diluents for dry formulation have the property of surface acidity, which catalyzes the decomposition of many organic pesticidal chemicals. The surface acidity must be neutralized to overcome the catalytic activity. The deactivators are usually organic compounds which share or contribute a pair of electrons to the acid sites of the catalytically active substance. These organic compounds are ethers, glycol ethers, ketones, esters, amines, acid amides or sulphoxides.[4] Examples of paired electron compounds shown in figure 4 are diethylene glycol and HMT. It is not sufficient, however, to select the organic compound at random, because pesticidal chemicals may have different mechanismus for decomposition and structural characteristics that are incompatible with the potential deactivators.

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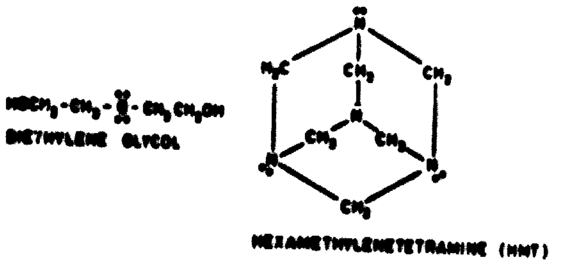
[4] Fowkes, F. M., *et al.* (1960) *Journal of Agricultural and Food Chemistry*, Vol. 8, p. 203.

Figure 4. Deactivators for pesticide formulation



Study of the effect of oxygenated materials, such as ketones, glycols and alcohols, as deactivators for heptachlor formulations [prepared upon attaclay (an attapulgite), Barden clay (a kaolinite) and other minerals] showed that all of the compounds functioned effectively as deactivators for heptachlor-clay systems with the effectiveness diminishing in those materials having a relatively high volatility.[5] Urea is an effective deactivator for many of the clays and minerals used in aldrin formulations.[6] Attempts to use urea in a similar manner for heptachlor formulations were not equally effective; there seems to be incompatibility between the system heptachlor-urea and the acid sites of the clays.

Other work has shown that hexamethylenetetramine (HMT) is a preferred deactivator for endrin formulations. However, when endrin is formulated with methyl parathion, a neutral-type deactivator such as diethylene glycol gives the best results. Fatty acids, such as tall oil acids, are effective deactivators for methyl parathion on attapulgite.[7]

Anti-caking agents

When dust concentrates, wettable powders and granular formulations are prepared in concentrations close to or at the saturation point of the carriers, caking occurs in storage when the individual particles of the formulation become stuck or fused together to form lumps or a solid mass which resists minimal physical effort to break it. When dry formulations of liquid pesticidal chemicals show a tendency toward caking, it is because the surface film of the liquid forms an adhesive bond. Caking of dry formulations of normally solid pesticidal chemicals (especially those prepared by impregnation of a solution or molten pesticidal chemical) often occurs after the mass has cooled and crystallization takes place at the particle interfaces.

The addition of anti-caking agents to a formulation will prevent the formation of an adhesive or a physical bond between the particles. In the formulation of dry pesticides, diatomaceous earth and microfine synthetic silica and silicate are often used as anti-caking agents. Finely divided clays, such as attapulgite are often useful for this purpose. The requisites for the anti-caking agent are low bulk density and high sorbency. Fine particle size and high surface area are significant. Anti-

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[5] Malina *et al., op. cit.*

[6] Fowkes *et al., op. cit.*

[7] Sawyer, E. Jr., and J. Plon (20 November 1960) United States Patent 2,962,418.

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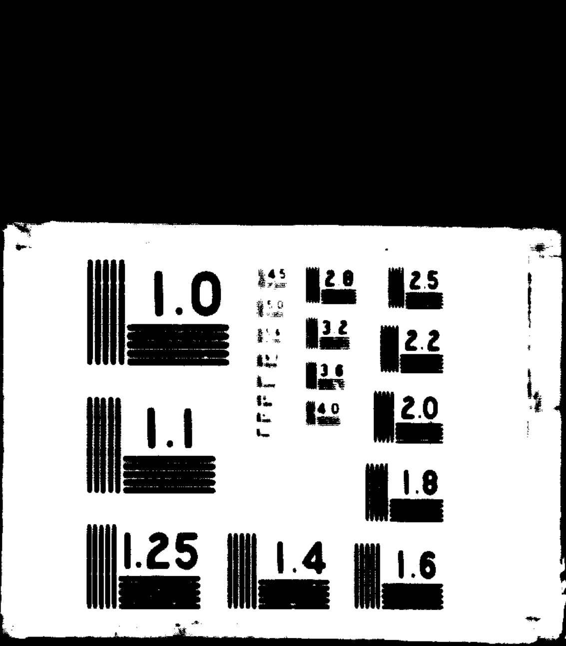

caking agents should furthermore be insoluble in any of the organic or liquid phases of the formulation.

Dry lubricants

Dry lubricants improve the flow or the slip characteristics of the formulations. Although anti-caking agents may assume part of this function, there are applications for dry, seed-treatment compositions where the use of the formulation must not interfere with the plantability or flow of the seed from the seed hopper through the metering orifice. Materials useful as dry lubricants in pesticide formulation are powdered graphite, soapstone talcs and certain metal stearates.

Protective colloids

Protective colloids are used in liquid formulations or aqueous dilutions of wettable-powder formulations to inhibit the agglomeration and sedimentation of dispersed particles. They generally have high molecular weight or are polymeric materials that are soluble or dispersible in the continuous phase of the suspension. They function by one or both of the following two mechanisms: by increasing the viscosity of the continuous phase and by imparting a similar electrical charge to all of the dispersed particles. Typical materials used as protective colloids are polyvinyl pyrrolidone, sodium carboxymethylcellulose, methylcellulose, blood albumin and collagen. The water-swelling bentonites, such as the type mined in Wyoming, are inorganic protective colloids.

Stickers

Stickers are adjuvants which can be added to a formulation concentrate, although more commonly, they are added to a spray tank prior to application. They prevent the run-off of spray solutions when applied to crops. After the evaporation of water or solvent, stickers retard the wash-off of the pesticide deposit on the plant by wind or rain. Although many protective colloids and gelling agents, such as blood albumin, are used as stickers, other preparations, such as polyethylene polysulphide known commercially as PEPS, can be used. A number of proprietary compositions are used as stickers, but they are generally intended for tank-mix application and not for incorporation in the formulation concentrate.

Anti-dusting agents

Anti-dusting agents reduce the dustiness of wettable-powder and granular formulations. They are generally liquid substances which cause extremely fine particles of dry materials to adhere to each other, thus making them less susceptible to air flotation and drift.

Many wettable powders contain active ingredients which are extremely hazardous to operators who handle them. These hazardous materials can include thiophosphates, which are used in orchard sprays, or mercurial fungicides, which are often used in seed-treating formulations. In order to protect the operator, these materials are treated with a liquid agent (frequently a water-soluble material such as glycerine) to suppress the dustiness. After adding the formulation concentrate to water, the anti-dusting agent should not interfere with the efficacy of the product.

Granular pesticides, which are usually shipped in multiwall bags, are frequently subjected to mechanical attrition during handling or shipping; a resulting fine powder is caused by erosion from the edges and corners of the granular particles. Such fines are undesirable because they may become airborne during application and drift upon adjacent fields. This drift can result in possible injury to the adjacent crop if the granular pesticide is a herbicide or leave undesirable residues as with insecticides. Water soluble materials, such as glycerine or petroleum oil (diesel oils, SAE No. 30 motor oil or crankcase drippings) may be used to minimize dustiness from fines.

Anti-foaming agents

Anti-foaming agents are surfactants which suppress the tendency of foam formation by other surfactants used as emulsifiers or wetting agents when the formulation is diluted with water. Foam is undesirable in spray tanks, especially those using a by-pass agitation, because it interferes with the development of sufficient pressure at the nozzles for proper spraying. To overcome the tendency of excessive foam, anti-foaming agents are added to the concentrate or to the spray tank. The anti-foaming agents are proprietary compounds, such as liquid silicone or aliphatic alcohol of eight to ten carbon atoms in length.

FORMULATION DESIGN AND EVALUATION TESTS

The large range of physical and chemical properties of different pesticidal chemicals has been discussed previously. Therefore, the cost for preparing a given type of formulation will vary according to the properties of the pesticidal chemical. When a given pesticidal chemical cannot be formulated inexpensively as an emulsifiable concentrate for spray application, an alternative choice would be a wettable-powder formulation. Similarly, some chemicals do not lend themselves readily to the formation of impregnated granules; therefore, an alternate technique, such as extrusion or pan granulating, should be considered. The cost of pesticide formulation reflects the properties of the pesticide and the performance characteristics of the formulation required for optimum control of the pest.

Liquid formulation

Liquid formulations are among the most popular formulation types. As a general group, recommended dosages of liquid formulations are easily computed and dispensed. When realistically conceived, emulsifiable and similar liquid concentrates are economical formulations since they can be readily diluted with water and conveniently applied. Regardless of type, liquid formulations all have one requirement in common, i.e. the solvent or the fluid diluent must be physically compatible with the active ingredient under all conditions of storage. Experimental procedures for developing liquid formulations are described in detail and in their relative order of importance.

Emulsifiable concentrates

Emulsifiable concentrates consist of the toxicant, the solvent and the emulsifier. The solubility characteristics of the pesticidal chemical determines the solvent or solvent type to be used and the concentration which is permissible for meeting certain storage conditions. At any given concentration, the physical nature of the pesticidal chemical-solvent combination determines the type of emulsifier and emulsifier balance to be used. The stepwise selection of solvent and emulsifier is the initial phase of emulsifiable concentrate development.

Solvent selection and solubility determination. The first step in the formulation of an emulsifiable concentrate is to estimate the solubility of the toxicants in suitable solvents. A solvent from each of the following classes should be tested: kerosene, xylene-range solvent,[8] heavy aromatic naphtha and cyclohexanone.

Because commercial solvents vary in their properties, it is desirable to know precisely the density, boiling range and per cent aromatics of a test solvent. A simple procedure for approximate solubility determination is described in which the quantities are fairly small to conserve the toxicant, but other suitable units may be substituted. The following equipment is required:

Burettes (5 to 25 ml) or pipettes (2 ml);
Balance with sensitivity of 0.01 g;
Five, medium-sized test tubes;
Hot water bath;
Refrigerator.

The experimental procedure is as follows:

(1) Weigh 1.20 ± 0.02 g of a representative sample of the toxicant into each of five test tubes.
(2) Into each test tube, pipette 2 ml of one solvent.
(3) Each test tube is warmed gently, if necessary, to effect solution.
(4) To test tubes where solution does not occur, add another 2 ml of solvent and repeat the mixing-warming process.
(5) To test tubes still containing undissolved solute, additional increments of solvent are added as in step (4) until 10 ml of solvent are consumed. If the solute is still undissolved, abandon further testing and choose another solvent.
(6) Place tubes containing dissolved solute in refrigerator set at 0° C. Observe evidence of any crystallization or stratification after four hours. Add seed crystals of toxicant to tubes which have remained clear.
(7) Add additional 2 ml increments of solvent to those tubes that have precipitated solute and repeat step (6) until 10 ml of solvent are consumed.

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[8] Such as xylene 5° or xylene 10°. Range refers to boiling-point range; the smaller the range is, the purer is the solvent.

Data interpretation is carried out using the following illustrative format:

Solvent consumed (ml)	*Approximate equivalent (lb/gal)*	
	Room temperature	*0° C.*
—	5.0	5.0
2	2.5	2.5
4	1.67	1.67
6	1.25	1.25
8	1.0	1.0

This test is the basis for more exact solubility measurements with the most suitable solvents.

Calculation and laboratory preparation of emulsifiable concentrates. It is important that a representative sample of the technical pesticide be used for all trial formulations prepared for cold-stability tests or emulsification tests. The presence of impurities can seriously affect the solubility and cold-stability properties, density of the finished formulation and selection of the emulsifier balance.

The concentration units for emulsifiable concentrates used principally in United States agriculture are expressed as lb of active ingredient/gal. Because of a significant coefficient of cubic expansion for most liquid pesticide formulations, it is necessary to establish the concentration at a specified temperature. For most purposes, the temperature reference point of 20° C has been found to be satisfactory. The calculation of emulsifiable formulation is complicated by the fact that the United States federal and state regulatory authorities judge formulations on a weight per cent basis instead of weight/unit of volume. The quantity of emulsifier to be used is calculated as a weight per cent.

Plant formulation is generally accomplished using pounds and/or gallons as units of measurement with the final plant formulation being measured in gallons. Since pounds and gallons are too large units for laboratory preparations, it is necessary to convert to standard laboratory units of measurement (i.e. g/cm^3). The mathematics of this conversion is as follows:

$$1 \text{ pound} = 454 \text{ g}; \ 1 \text{ gal} = 3{,}785 \text{ ml}.$$

Since 100 ml is an adequate volume for a laboratory formula, the calculated concentration on a weight/volume basis is as follows:

$$\frac{454 \text{ g}}{3{,}785 \text{ ml}} \, 100 \text{ ml} = 11.994 \text{ g} \simeq 12 \text{ g}.$$

Thus, 12 g/100 ml is equivalent to 1 lb/gal or 1 kg/ha.

The laboratory procedure for preparing a liquid pesticide formulation is described when considering weight/volume (lb/gal). The following equipment is required:

Graduated glass-stoppered cylinder (100 cm^3);
Triple-beam laboratory balance;
Hot plate to dissolve the toxicant;
Spatulas etc.

The experimental procedure is as follows:

(1) Weigh the empty, glass-stoppered graduate;

(2) Weigh into the graduate the calculated quantity of technical pesticide as required by the formulation being prepared and calculated as follows:

$$\text{technical pesticide (g)} = \frac{\text{pesticide weight (lb)/gal} \times 12}{\text{purity of technical pesticide (per cent)}};$$

(3) Weigh in the emulsifier on a per cent by weight basis;

(4) Add solvent to bring formula to 100 ml volume at 20° C; if heat is necessary to effect solution, cool before adding all of the solvent to final volume;

(5) Obtain net weight of formulation by subtraction; the resultant weight is the weight of formulation per 100 ml at 20° C. Note that for all practical purposes

$$\text{specific gravity} = \frac{\text{weight/100 ml at } 20^\circ\text{ C}}{100}.$$

To check the above calculations, the relations are given:

$$\text{weight of 1 gal of water} = 8.34 \text{ lb},$$

$$\text{specific gravity} \times 8.34 = \text{weight 1 gal formulation (in lb)},$$

$$\text{lb of pesticide/gal} = \text{weight 1 gal formulation} \times \text{per cent pesticide} \times \text{per cent assay}.$$

The per cent by weight for each formula component is calculated as follows:

$$\frac{\text{weight of component}}{\text{net weight formulation}} = \text{per cent component}.$$

The per cent of all components should total 100 per cent.

The conversion of laboratory data to production batches is carried out as follows:

(1) specific gravity × 8.34 (weight/gal of water) = weight/gal of formulation,

(2) weight/gal of formulation × number of gal = weight/batch,

(3) per cent weight of component × total weight/batch = weight component/batch.

This method of calculation is not entirely satisfactory if the emulsifier content is to be as exact as possible, since the final weight of the formulation must be estimated. In desk calculations of formulations, this becomes even more troublesome, particularly with multitoxicant systems. To overcome this difficulty, a multitoxicant calculation system has been designed for fairly precise estimates of weight percentages of formulations.[9]

Emulsifier selection. In selecting the appropriate emulsifer for the concentrate, the formulation chemist must have the co-operation of the biological field research worker or the potential user to answer the following questions:

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[9] Lindner, P. (1966) *Farm Chemicals*, April issue, pp. 50—57.

At what dilution rate will the formulation be applied?
What water hardness range must be considered?
Is the water diluent temperature likely to be unusually warm or cold?
Will agitation of the emulsion be available?
Are any specific properties such as rapid spontaneous dispersion, long stability or excellent reconstitution particularly important?

The selection of an emulsifier or an emulsifier blend for an emulsifiable concentrate is one of the least understood aspects of pesticide formulation. There are many variables which can affect the performance of an emulsifier during the act of emulsification or dilution with water. The following questions may be asked: Why is not one emulsifier as good as another in a given formulation? After finding a good emulsifier blend for a particular formulation, cannot the emulsifier be used with equal success in another formulation? The answer to these valid questions is that a good or well-balanced emulsion involves the selection of an emulsifier blend whose average structure reflects the polarity of both the discontinuous (oil) and continuous phases (water). Both toxicants and their solvents vary considerably in their polarity; in the terminology of the formulation chemist, they are more or less hydrophilic (water-soluble) or lipophilic (oil-soluble).

The following lists of solvents and toxicants rank them from lipophilic to hydrophylic properties:

Solvent	*Toxicant*
Refined kerosene	Malathion
Kerosene (plant)	Parathion
AR solvent (methylated naphthalene)	Heptachlor
Heavy aromatic naphtha	Aldrin
Espesol 3B	Chlordane
Espesol 5	DDT
Xylene 5°	BHC
Toluene	Lindane
Ketone (isophorone)	Dieldrin

A simple explanation of the mechanism of emulsifiers is that they reduce the interfacial tension between oil and aqueous phases thus permitting one of the phases (usually the oil) to disperse into very fine discrete particles within the continuous (water) phase. If all other factors are equal, the better the reduction of the interfacial forces, the smaller will be the average size of the discrete oil particles. The size of these oil particles governs the relative rate ot undesirable creaming of an emulsion. For example, the larger the average oil particle size, the more rapid will be the rate of creaming.

The second function of the emulsifier is to surround each particle with a similar repellant electrostatic charge and to prevent these small discrete particles from colliding and recombining into larger particles, accelerating the rate of creaming and eventually coalescing into a second continuous phase or "oiling out". In reality, no such sharp distinction exists between these two functions, but it helps to explain some anomalous behaviour of emulsions. For example, an emulsifiable concentrate may show excellent, spontaneous dispersion but poor stability on standing; other emulsions seem to produce much creaming but never oil out, while still other emulsions oil out with little prior evidence of creaming.

These theories would be more helpful if they aided in the selection of effective emulsifiers on the basis of prior calculations of interfacial tension, polarity or the hydrophile-lipophile balance. Although impressive attempts have been made to use the theories, the selection of emulsifiers remains a trial-and-error process.

The development of paired-emulsifier systems is an aid to efficient formulations. Paired emulsifiers roughly reflect the approximate hydrophile side of a class of toxicants. Each member of the pair differs sufficiently in the hydrophile side, however, so that proper blending of the two enables the formulation chemist to produce a balanced formulation of virtually any of the toxicants in the class at any concentration and with any of the more commonly used solvents. There are a number of paired systems marketed, which the formulation chemist should have available for testing work.

The simplest approach to determine the appropriate balance of an emulsifier pair is the preparation of two samples of the test formulation. Each sample should contain a member of the pair in an arbitrarily selected quantity (usually 5 per cent). Blends in ratios of 0:5, 1:4, 3:2, 2:3, 4:1 and 5:0 are tested preferably at practical dilutions in one or a series of water samples of varying but precisely known hardness. After this initial screening is complete, more exact ratios may be derived for optimum performance. Although the standards are somewhat arbitrary, it is generally unsatisfactory for a formulation to oil out within a 2-hour period, and the rate of creaming should not exceed 3 to 5 per cent of the emulsion. In selecting the proper emulsifier pair, it is wise not to select a combination that is too sensitive to slight shifts in the ratio of the pair. In any production sequence, the quantities of toxicant, solvent and emulsifier will vary. The system must be able to handle these variations without large changes in performance. It is more desirable to reduce performance factors in favour of a more adaptable system.

A word of caution concerning the accuracy of the emulsion tests is extremely important. The tests must be performed consistently, especially in regard to water temperature, the manner of adding the concentrate to the water, and the type and duration of agitation. If not carefully controlled, all of these factors cause a significant variation in the results obtained in the test.[10]

Occasionally, it may be necessary to correct the balance of an already prepared batch or to make other adjustments. It is helpful to know in which direction to proceed. The following generalizations may be helpful in such cases:

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[10] Behrens, R. W. and W. C. Griffen (1953) *Journal of Agricultural and Food Chemistry*, Vol. 1, p. 720.

Effects of increasing the ratio toward the lipophilic side	*Effects of increasing the ratio toward the hydrophilic side*
Improve performance in soft water;	Improve performance in hard water;
Increase tendency to oil out;	Increase tendency to heavy creaming;
Provide better stability at higher dilution rates;	Improve stability at lower dilution;
Improve performance in cool water;	Improve performance in warm water;
Improve spontaneity.	Increase aging stability.

Storage stability. The useful product life of an emulsifiable concentrate depends on the mutual compatibility of toxicant, emulsifer, solvent, container, dissolved mineral salts, the moisture which may be present in small quantities and the over-all resistance to oxidation. All toxicants deteriorate after a certain time. They usually release acidic products, which, in turn, may accelerate the degradation of the emulsifier or the container. The storage life can sometimes be prolonged by the use of stabilizers such as epichlorohydrin.

Since it is usually impractical to wait several months or years to establish the shelf life of a product before marketing it, the formulation chemist performs storage tests at elevated temperatures. Ideally, the accelerated storage tests are run at series of elevated temperatures; if the reaction order remains constant throughout this range, the stability can be predicted with a fair accuracy at ambient temperatures through the use of the Arrhenius equation. The more usual practice, however, is to make a working assumption regarding the relationship of storage at one elevated temperature to actual shelf life. For example, a commonly used relationship is that one month at 50° C is the equivalent of two years at ambient temperature.

Storage tests should be carried out in the proposed container with control samples in glass containers. At the conclusion of the test, the toxicant assay, emulsification properties and acidity should be determined and compared with data obtained from a freshly prepared sample. The formulation should be examined for stratification or precipitation, and the container should be checked for corrosion.

Tests of cold-storage stability should be run concurrently with the accelerated storage tests. For cold-storage testing, small glass bottles or vials of approximately 4- to 5-dram capacity are fitted with tightly closed stoppers. Approximately 8 to 10 ml of trial formulation is placed in each test vial. The studies should be carried out at temperatures of —24°, 0°, 7° and 20° C. The samples are seeded at the end of the third day and checked on the tenth day. If crystallization is noted at one temperature but not at the next higher temperature, the solubility is satisfactory at some temperature between those limits. If there is slight crystallization at 0° or —24° C, it is sometimes possible to find a solvent (if xylene or heavy aromatic solvents are being tested) with a higher percentage of aromatics or a higher kauri-butanol number. If the higher grade solvents are not satisfactory, the solvency of the system may be upgraded by the addition of small quantities of cyclohexanone. The concentrations and temperature limitations of typical commercial products are as follows:

	Cold stable concentration (lb/gal)	*Concentration (lb/gal)*	*Temperature limit (°C)*
Heptachlor	2.0	3.3	10
Aldrin	2.0	4	10
DDT	2.0	3	50

Many formulations are unstable in the presence of iron or are themselves of a corrosive nature and degrade the container causing leakage. As a consequence, the steel pails and drums commonly used for emulsifiable formulations are lined with protective coatings, which are mixtures of phenolic and epoxy resins. Coatings with a high phenolic content are more resistant to acidic corrosiveness than those formulated on the epoxy side, but they suffer the drawback of being very brittle. This characteristic results in the breaking of the coating frequently when the pail or drum is dented and exposes the steel. Therefore, it is economical to select a lining with the highest epoxy content that the corrosiveness of the concentrate will permit.

Oil concentrates

Oil concentrates are similar in dimensions to emulsifiable concentrates. They are intended primarily for dilution with a low-cost miscible oil such as kerosene, diesel oil or fuel oil before field application, and do not require an emulsifier. Occasionally, the oil concentrates are used to mix pesticides with dry fertilizers or to impregnate dust or granules.

The procedures for solvent selection with oil concentrates are the same as those for emulsifiable concentrates. Acceptability is based upon cold stability at a reasonable or practical concentration. When intended for field dilution with an oil, the ease of miscibility with typical oils should be tested at practical dilution rates. Although the formation of a precipitate after dilution is seldom, its presence indicates that the solvent lacks sufficient coupling power or that the concentration of the active ingredient must be reduced.

Normally, oil concentrates are not as corrosive to container linings as the emulsifiable concentrates. They should, however, be tested with strips of mild steel or tin plate under accelerated storage conditions. Functional characteristics of specific gravity and flash point should be determined.

Aqueous concentrates

Aqueous pesticide concentrates are water solutions of salts of organic acids (usually herbicides, which include dicamba, 2,4-D and 2,4,5-T). They are mainly dimethylamine salts, although sodium, potassium or lithium salts are sometimes used.

Solvents. Because water is the solvent used for aqueous concentrates, there is a definite solubility limitation to the concentration of active ingredient contained in the solutions depending upon the cation. The dimethylamine salts generally give adequate cold stability as well as good performance in the field.

Effects of hard water. Some organic carboxylic acids, such as 2,4-D, 2,4,5-T and MCPA form insoluble salts in the presence of cations, such as calcium and magnesium found in hard water. Dicamba does not present this problem. Water hardness, however, can be overcome by the use of chemical sequestering agents added to the concentrate or to the tank at the time of field dilution. Among the sequestering agents are sodium polyphosphate, ethylenediamine tetracetic acid and its derivatives, and citric acid salts. Some lignosulphonates have been used as sequestering agents to prevent precipitation of the active agent by hard water. When iron is present in the water in quantities exceeding several parts per million, sequestering agents related to ethylenediamine tetracetic acid are used.

Acidity and pH. The addition of base to the herbicidal acids in stoichiometric quantities will produce solutions having different pH values that are usually alkaline because the acid strength, ionization constants and acidic impurities of herbicidal acids vary. The stronger the acid, the closer the pH value is to 7. If dimethylamine is used as the base of the salt, an excess will result in a product with an objectionable amine or fish-like odour.

Storage and stability. The herbicidal acids are generally quite chemically stable in aqueous concentrates of their salts; however, accelerated storage tests should be run for any new herbicidal acid or aqueous concentrate in the normal manner at 50° C for periods up to 90 days. The packaging of aqueous concentrates of herbicidal acid salts in metal containers often presents problems of corrosion. For pails and drums, however, pigmented, high-baked phenolic linings as well as modified epoxy linings overcome some of the difficult problems of container corrosion. For small packages up to one gallon in size, high-density polyethylene bottles and jugs are satisfactory.

Evaluation of functional characteristics. Aqueous concentrates may be characterized by a specific gravity determination. Aqueous concentrates are subject to freezing at very low temperatures. Banvel 4S is the 4 lb/gal concentrate of dicamba dimethylamine salt; it will freeze at approximately —20° C. However, when warmed to room temperature, the properties of the formulation are unchanged.

Dry formulation

Dry formulations include dust bases, wettable powders, dusts and granules. Dry formulation of a new pesticide chemical requires prior study of its compatibility with typical carriers and diluents.

Dust bases

Dust bases must be dry, finely divided and flowable powders. They must be capable of easy dilution with a variety of inert powdered diluents to produce a uniform dusting powder. They must be sufficiently high in concentration to permit economical storage and shipment and with concentration dimensions which will allow simple calculation for the dilution process. They must be non-caking and remain flowable under all conditions of storage. They must be chemically stable in storage for several years under normal storage conditions. If deactivation is carried out as above to permit 5 per cent or less decomposition for 90 days under accelerated conditions, this requirement is generally met.

Stability studies and deactivation. A practical method is to prepare a 5 per cent dust formulation of a number of typical mineral carrier and diluent classes such as diatomaceous earth, attapulgite, montmorillonite, kaolinite, pyrophyllite, talc and calcium carbonate or powdered limestone. A convenient quantity to handle is 250 to 500 g of the finished product. The active ingredient can be mixed in a beaker of suitable size by a slow-speed paddle stirrer or simply with a flat metal spatula. If the pesticidal chemical is a liquid, a porcelain mortar from 15 to 20 cm in diameter and a matching pestle generally provide good mixtures. The crude mixtures thus prepared are ground further in a laboratory grinding mill. After grinding, the pulverized product is blended in a jar tumbler or in a pint- or quart-sized, twin-shell blender. The material is then separated into several portions and a small quantity sufficient for the initial chemical analysis is withdrawn.

One portion of the preparation is precisely labelled and subjected to room-temperature stability studies. The other portions are placed in a constant-temperature oven at elevated temperatures for accelerated-storage tests. After 7, 14 and 28 days from the beginning of the accelerated-storage tests, small samples of the 5 per cent dust formulations are withdrawn and analysed for active ingredients. The results of analysis are compared with the results of the initial assay of the formulation and the rate of decrease in active ingredient content after each storage period to indicate chemical incompatibility. If decomposition at the end of the 28-day period is less than 1 or 2 per cent of the active ingredient initially present, accelerated-storage tests are continued for two and three months.

Decomposition proceeds at a faster rate with the more absorbent clays such as montmorillonite and attapulgite. Some of the less absorbent materials contain highly surface-active impurities that cause rapid decomposition. Diatomaceous earth, even though generally more absorbent than attapulgite and montmorillonite, does not normally possess the surface acidity associated with the clays, therefore, catalytic decomposition occurs at a lower rate.

The decomposition of pesticides incorporated with dry mineral carriers occurs by one or more of the following principal mechanisms: catalytic decomposition resulting from surface acidity, the acidity or alkalinity of the carrier or diluent and thermal effects. If the rate of decomposition follows approximately the absorbency of the carriers or diluents (with the exception of diatomaceous earth), catalytic surface acidity is certainly involved in the decomposition rate. However, if the rate of decomposition is greater for the attapulgite or montmorillonite carriers, the pH value of the carrier is involved.

Attapulgite is slightly alkaline and montmorillonite is acidic. Therefore, if the rate of decomposition with attapulgite is greater than that with montmorillonite, the active ingredient is very probably sensitive to mild alkaline reactions. If the active ingredient decomposes at a very low rate or not at all with talc and pyrophyllite but at a significant rate with montmorillonite and attapulgite, the catalytic surface acidity is involved. If, however, the rate of decomposition with talc and pyrophyllite is significant and nearly equal to that found with diatomaceous earth as well as with kaolinite, attapulgite and montmorillonite, the active ingredient is thermally unstable at least at the elevated temperature of the tests. An additional cause of decomposition or decreasing assay is hydrolysis in the presence of moisture or volatilization.

Volatilization is usually a minor factor which can be minimized by conducting the storage tests in small, tightly closed containers. The effect of moisture can be verified by preparing a 5 per cent dust on a carefully dried sample of talc or pyrophyllite and conducting parallel tests with the same diluent to which small increments of 0.5 per cent or more of moisture have been added.

A word of caution concerning the accuracy of the assay method of testing is advisable at this point. Because laboratory stability studies must be based upon chemical assay methods, it is necessary that all aspects of the assay method be fully developed before chemical compatibility and stability studies are undertaken. Most assays of dry formulations are based upon the analysis of a solvent extract of the active ingredient from the carrier or diluent. This extract is then usually analysed by chemical, infra-red or other spectro-chemical methods or gas chromatography. In these steps of the assay procedure there is seldom any great difficulty. However, the accuracy of the assay procedure is dependent upon the accuracy of the extraction procedure. Difficulties often can be encountered because the extraction solvent must be capable of dissolving a significant quantity of the active ingredient, and the solvent should be capable of displacing any active ingredient which has been absorbed by the diluent or carrier particles. It has been observed that polar molecules such as dicamba are very strongly absorbed by some clays such as attapulgite. Therefore, in order to displace them, a more strongly polar solvent such as acetone or alcohol may be necessary to effect a complete extraction.

In all stability studies, it is desirable to determine the identity of decomposition products when instability of the active ingredient is observed after accelerated-storage tests. A complete analysis of the experimental formulation to obtain a material balance follows. If an experimental formulation is found by assay to contain only 70 per cent of the initial active ingredient, the remaining 30 per cent of decomposition products should be identified and measured quantitatively.

Carrier selection and concentration limits as a function of physical properties. The most important physical properties of a technical grade pesticidal chemical which determine the selection of the carrier used in dust bases are the physical state, the melting point and the specific gravity. The simplest materials to handle are the powder or crystalline pesticidal chemicals with melting points of approximately 90° to 100° C. Among the most difficult materials are low-melting solids because their waxy nature prevents convenient handling of them as solids. Although the liquid pesticidal chemicals can be incorporated with absorbent carriers by a straightforward spray-impregnation method, the necessary equipment is more complex to install and control than the equipment for dry-powdered pesticidal chemicals.

The most important properties of a carrier for dust bases are sorptivity, pH and surface acidity. When formulating powdered, high-melting pesticidal chemicals, however, sorptivity is of little or no importance because the active ingredient can be combined with the carrier by a simple dry-blending process and the mixture reduced to the desired particle size by mechanical grinding. There is generally no serious problem in attaining high concentrations of the active ingredient in dust bases with pesticidal chemicals having melting points above 100° C. Indeed, with such materials even less sorptive diluents such as talc and pyrophyllite may be used. Fortunately, these diluents of low sorptivity generally have a low surface acidity so that only small quantities of deactivator are necessary. These diluents are fortunately much lower in cost than the more absorbent carriers. Pesticidal chemicals having high melting points can be readily and more economically formulated than liquid or low-melting, solid pesticidal chemicals.

It was pointed out earlier that the sorptive capacity of a mineral carrier is inversely proportional to its bulk density, and that the sorptivity of a given liquid in per cent by weight of finished formula is directly proportional to the density or specific gravity of that liquid. In other words, a clay which can be used to formulate a dust base having 40 per cent chlordane of specific gravity 1.6 can only contain up to 25 to 30 per cent of a liquid pesticide having a specific gravity of 1.5 to 1.2. Therefore, the chlordane sorption value of the carrier should be known as well as the density of the liquid pesticide with the carrier relative to that of chlordane. To determine the chlordane sorption value, the "rub-out" sorption test can be used.

Two additional factors that limit the percentage of active ingredient which can be formulated with absorbent carriers in dust bases are the assay or active equivalence content of the technical pesticide and the quantity of solvent which must be combined with the technical pesticide to efficiently incorporate the active ingredient with the carrier. For example, technical methyl parathion normally contains 80 per cent active ingredient. Therefore, to prepare a 25 per cent dust base, it is necessary to use the ratio 25/0.80 or 31.25 per cent of technical methyl parathion in the formulation. Similarly, to prepare a 25 per cent heptachlor dust base from a technical heptachlor assaying at 74 per cent, it is necessary to use 33.8 per cent of the technical heptachlor. Because technical heptachlor is a low-melting waxy solid, it is convenient to melt it and add a small quantity of solvent to improve handling and spraying characteristics. Thus the quantity of liquid to be sprayed upon the carrier is increased to between 37 and 40 per cent.

Technical chlordane, on the other hand, is a liquid used on a 100 per cent active ingredient basis. Its sprayability can be improved by slight warming to reduce the viscosity. Because of its high specific gravity, chlordane can be readily formulated up to a 40 per cent active ingredient concentration on absorbent carriers, such as attapulgite or diatomaceous earth.

Chlordane and toxaphene are among the few liquid or low-melting, solid pesticides which can be formulated in concentrations of 40 per cent or higher on simple carriers such as attapulgite. The reason is their high specific gravity and the fact that they are liquids or very low-melting solids with a high degree of solvency or miscibility in solvents such as kerosene. If a high concentration such as 40 per cent active ingredient is required for pesticides as in heptachlor, it may be necessary to use diatomaceous earth and to supplement the absorbency of the carrier by the addition of highly absorbent such as synthetic silica. Such formulation prepared from technical heptachlor and using an auxiliary solvent will contain 65 to 70 per cent liquid. Because synthetic silica is a relatively expensive material, it is seldom used as a primary carrier but is frequently used to upgrade the absorbency of natural clay.

Storage stability. Accelerated storage stability should be determined on the finished formulation by placing the sample in a sealed container in an oven maintained at 50° C. Assays should be made on the initial sample and after 30 days' storage. Duplicate analysis should be made of both the initial and the aged samples. The average loss in 30 days determined by an assay should be less than 2 per cent.

It is important that the formulation exhibit non-caking tendencies when stored at 50° C for 24 hours under a static pressure of 25 g/cm^2. This is determined by measuring the percentage of the powder retained on a 100 mesh (United States standard sieve series) or 149 μm screen using a Tyler Ro-tap sieve analysis machine.[11] The quantity retained on the 100 mesh screen should be less than 5 per cent of the quantity that is retained on a sample of the same formulation which has not been subject to accelerated storage tests.

Wettable powders

Wettable powders generally have the same concentration units (percentage by weight) as the dust bases of the same pesticide. Wettable powders are similar in appearance and have approximately the same bulk density, but there are functional differences in their use. Dust bases are generally diluted with a dry, powdered inert such as talc or pyrophyllite, while wettable powders are primarily diluted with water for a spray formulation. Although it is possible to dilute a wettable powder with talc, pyrophyllite or other inert material to make a dust formulation, the wettable powders have additional functional ingredients and more rigid specifications which make them more expensive than dust formulations.

Stability studies and deactivation. Because wettable powders are special forms of dust concentrates, the procedures for determining stability and the necessary quantity of deactivator to prevent decomposition are the same as for the dust concentrates. Certain wetting agents can function as deactivators. However, they are used in small quantities and only partially deactivate the formulation.

Carrier selection and concentration limits as a function of physical properties. The formulation of wettable powders is similar to the formulation of dust bases since absorbent attapulgite, montmorillonite or diatomaceous earth carriers must be used for liquid and low-melting pesticides. For the medium to high-melting pesticides, however, highly absorbent clay or material with low ab-

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[11] Ro-tap is the registered trade mark of the W.S. Tyler Co., Cleveland, Ohio. A description of this machine is given by World Health Organization (1961) *Specifications for Pesticides*, 2nd edition, p. 521.

sorbency such as talc, kaolinite and pyrophyllite must be used as diluents. The detailed discussion of these points for dust bases is applicable to wettable powders.

Storage stability. It should be tested by accelerated storage. The suspendibility and toxicant stability of a wettable powder should be controlled after the storage test.

Wettability and suspensibility. The wettability of the powder is the time required for a given weight of the formulation to be completely wet and submerged beneath the water surface. The shorter the period of time (in seconds) required for wetting, the better is the wettability of the formulation. In addition, a wettable powder must remain uniformly suspended and free of nozzle-plugging agglomerates in the mixing tank throughout the application period.

The stability of a suspension of solids is dependent upon a balance of several forces. Stokes' law indicates that stability is favoured by increasing the viscosity of the suspending medium or by reducing the size of the particle. Therefore it is desirable to reduce the particle size as much as possible by a suitable milling operation. Unfortunately, as the size of a particle is reduced, the small attractive forces on its surface become significant with respect to the particle's mass. This effect causes the joining together of several particles into larger agglomerates, which settle more rapidly because of the increased size and thereby plug nozzles. Occasionally, this behaviour results in the formation of a flocculent curd in the suspending medium.

To prevent agglomerate formation, surface-active materials are introduced into the formulation as suspending or dispersing agents. They surround each particle with a like electrostatic charge and cause a reorientation of the molecules surrounding the particle into an electrical double layer. This layer develops a potential with respect to the rest of the system, which wards off collisions with other particles. Wetting agents reduce the interfacial tension between the powder and the suspending medium.

The suspension characteristics of the formulation may be improved by increasing the viscosity of the medium. In practice, sodium carboxymethylcelluose, polyvinylpyrrolidone and other water-soluble polymers are added to wettable powders. However, when added to water, these materials have little effect upon the viscosity because of their low concentration. Certain formulations benefit from their addition possibly due to the formation of a protective colloid around the particles to prevent agglomeration and settling.

Surfactant selection. This is primarily an empirical process. Surfactant systems used in the formulation of wettable powders usually consist of a wetting agent and a dispersant. Wetting agents are generally sodium salts of alkylbenzene sulphonic acids, although non-ionics such as the polyethylene oxide derivatives of alkyphenols may sometimes be used. Other anionics such as alcohol sulphates and sodium sulphosuccinates provide good wetting performance. In some systems, however, these materials show excessive foaming tendencies. A number of trials are necessary before a satisfactory wetting agent is found. The dispersants are generally anionic materials and are frequently salts of lignosulphonic acids and sulphonated polyphenols. The quantity of wetting agent and dispersant generally used varies from 1 to 1.5 per cent each. Their ability to perform satisfactorily with a specific carrier pesticide combination is often very selective. The choice of the proper pair and ratio is based upon the results of selective testing of each wetting agent in combination with each dispersant. For example, if four wetting agents and four dispersants are selected from a number of typical compounds, 4×4 or 16 individual wettability and suspendibility tests are performed for the surfactant system at the same concentration level.

Procedure to evaluate the wettability. Weigh 0.5 of the experimental formulation on a 10 cm piece of glazed paper. Pour the powder rapidly but gently onto the surface of 100 ml of water contained in a 100 ml graduated cylinder. Measure the time with a stop watch from the moment the powder is placed on the surface of the water until 90 to 95 per cent of the material has become wet and submerged below the surface of the water. The time (in seconds) is the wetting time of the formulation.

Dusts

Pesticidal dusts are dry-powder formulations for application in the field without further dilution. Dusts are identical in appearance and general form to dust bases or concentrates. However, dusts contain a much lower concentration of active ingredient which may vary from 1 to 20 per cent. Pesticidal dusts are prepared by the dilution or cut-back of a dust or concentrate with a suitable inert powdered diluent or by directly combining the active ingredient with the diluent in the desired concentration.

A cut-back procedure requires a minimum of processing detail to obtain a uniform product. The cut-back process is preferable when dusts are made from pesticidal chemicals which are liquids or low-melting solids, or when powdered or high-melting, solid pesticidal chemicals are present in low concentrations of 1 to 3 per cent of the active ingredient.

If dust formulations are made directly from liquids or low-melting solids, a solvent is usually necessary to improve the spraying quality. The sorptivity of the diluent should be greater than that of the talc, pyrophyllite and calcium carbonate that is used. Possible absorbent diluents are attapulgite and montmorillonite, or kaolinite, which is somewhat less absorbent. One disadvantage of preparing dusts on absorbent carriers by impregnation is that often relatively large quantities of a deactivator are necessary to prevent decomposition of certain pesticidal chemicals, such as heptachlor and methyl parathion. If talc, pyrophyllite or calcium carbonate is the diluent in the cut-back procedure, deactivation of the carrier often is unnecessary, or at the most only 1 to 2 per cent may be required. A further advantage is that the low-sorbency diluents are frequently less than one-half as costly as absorbent carriers.

If pesticidal dusts are to be made directly from solids or high-melting pesticidal chemicals, the active ingredient should be as finely powered as possible. Furthermore, after deactivation and during the blending operation, representative samples should be withdrawn from various sections of the blender. The samples should be analysed for uniformity by assaying the active ingredient in each sample. Following blending by cut-back or direct blending, the finished mixture is ground by a suitable mill such as a Raymond mill or a micropulverizer and discharged into a blender to assure uniformity. As most diluents consist of very fine-sized particles, the grinding operation is not for particle size reduction but for obtaining a very thorough mixture of the active ingredient with the diluent to minimize segregation during storage and to assure a uniform product during the application.

Diluent selection. There is no generally accepted standard for the particle size or particle size distribution of diluents. The size generally ranges from 140 mesh (105 μm) to 270 mesh (53 μm); 90 to 95 per cent of some of the finer diluent products may even pass through a 325 mesh (44 μm) screen. However, for aerial application, the coarser dusts are generally more suitable because of lower drift than the extremely fine powders. For ground application to crops with a very dense foliage, a very fine dusting powder should be used to obtain a uniform coverage of all plant surfaces. Pyrophyllite is probably the most widely used diluent for pesticidal dusts. It is followed in popularity by talc and calcium carbonate. A number of other low-cost mineral-type diluents are used, e. g. dolomitic limestone and kaolinite have good sticking properties on plant surfaces. The low cost or local availability of diluents frequently affect the choice. The suitability of any diluent, however, should be determined by comparative field tests in the areas intended for their use.

Stability studies and deactivation. Even though many of the diluents, such as talc and pyrophyllite, have less surface activity and fewer acid sites than the more absorbent clays, their use in dilute dust formulations provides a relatively large number of active acid sites per unit of active ingredient. Consequently, the deactivation of the diluents to prevent decomposition during storage is necessary.

Evaluation of physical characteristics. To perform efficiently in dust application equipment, the flowability of the formulation is important. Generally, the flowability of a formulation prepared by liquid or low-melting, solid formulations either by cut-back or direct impregnation, decreases as the concentration of the active ingredient increases. The addition of 0.1 to 0.5 per cent of colloidal pyrogenic silica pigment improves the flowability. Because pesticidal dusts are metered volumetrically when applied by field dusting equipment, the bulk density of the product is important and must be controlled.

Granules

Most granular pesticides are produced by the spray impregnation of a pesticidal chemical or a solution of a pesticidal chemical upon an absorbent granular carrier. The maximum quantity of active ingredient which can be incorporated in this manner depends upon the sorptivity of the granular carrier and the purity and density of the pesticidal chemical or the density and the concentration of the active ingredient.

Pesticidal chemicals that have too low solubilities for formulation by impregnation may be processed into granular form by techniques based upon extrusion, pan-coating and pan-rolling. Although these techniques are used to some extent, they require specialized equipment that is not available to many formulators.

The two most important characteristics of granular pesticides are concentration and particle-size range. Although the maximum concentration is limited by the physical properties of the pesticidal chemical and the carrier, it is as low as 1.5 per cent for an endrin granule to as high as 40 per cent for a chlordane granule when granular attapulgite is the carrier. The particle size or particle-size range is normally based upon the selection of the properly sized carrier. Although granular pesticides range from 4 to 80 mesh, typical sieve size designations are 16/30, 20/40 and 30/60. One granular carrier used for special purposes is 20/25 attapulgite.

Other desirable characteristics of granular pesticides are storage stability, resistance against attrition, resistance against caking during storage and good flowability. The rate at which the granular releases the pesticide is difficult to control with impregnated pesticides. It is usually an inherent characteristic of the pesticidal chemical itself and the carrier. In actual practice, the release rates for different uses vary; each use must be treated individually.

An important requirement of granular pesticides is the uniform distribution of the active ingredient on all particles. To accomplish this by spray impregnation, spray nozzles must have an extremely low discharge rate. Rotary or tumbling mixing equipment should be used to minimize attrition of the particles.

Several types of equipment which are suitable for the laboratory development of granules are the double cone blender, the Patterson-Kelly twin shell blender and the Nauta mixer. They can be obtained in capacities of 2 ft^3 or less and can be fitted with an internal spray attachment. The liquid handling system consists of a spray tank with a capacity of 1 to 2 litres with an agitator and heating facilities. The liquid is carried to the spray nozzle either by a small gear pump or in a closed spray tank; it is pumped to the nozzle by compressed air or nitrogen. The liquid system should be capable of operating at 20 to 60 lb/in^2 pressure. To prepare formulations for which the spray liquid must be heated, all spray lines and the pump must be heated to prevent a drop in temperature of the spray liquid and to avoid crystallization. A fine filter with a particle size retention capacity less than that of the diameter of the nozzle is installed between the pump and the nozzle. To protect the pump from foreign particles, a 140 to 200 mesh basket strainer is placed between the spray tank and the pump. The positive-displacement, gear pump should have an adequate by-pass circuit and a throttling valve for pressure regulation and control.

Carrier selection. The principal carriers used in the formulation of impregnated pesticide granules are granular attapulgite and non-swelling montmorillonite. Kaolinite, pyrophyllite, talc and calcium carbonate have been tested as granular carriers, but they are generally too soft (suffering attrition during the impregnation process) or too low in absorbency. Swelling bentonite, which is a montmorillonite, is useful when high absorbency is not required. Granular vermiculite has many desirable properties for granular pesticides. However, because it has a relatively low bulk density, hoppers must be reloaded more frequently than is necessary for formulations based upon attapulgite or montmorillonite with the same concentration of the active ingredient.

Vegetable materials which have been studied and used to a limited extent are maize cob grits and crushed walnut and pecan shells. Maize cob grits have many desirable characteristics such as inertness, fair absorbency, resistance to abrasion and a bulk density of about 28 to 30 lb/ft^3.

The absorbency and catalytic surface acidity of all potential granular carriers should be studied. Because the sorptivity of a granular carrier is difficult to measure on a small scale, the carrier can be pulverized in a laboratory grinder and then the sorptivity is determined by the rub-out method. The sorptivity for granular pesticides is close to the chlordane absorption value as determined by the rub-out method. The catalytic surface acidity and the necessity for de-activation are determined by using the same test methods as for other dry formulations.

Typical particle-size ranges normally used for pesticide granules are 16/30, 20/40 and 30/60. These carriers should be tested to ensure that 90 per cent of the particles fall between the upper and lower limits of the particle-size range and the remaining 10 per cent are distributed randomly on either side. The maximum quantity permitted to pass through the finest screen should be specified because further attrition of the particles might conceivably occur during processing, bagging, shipping and handling, and result in undesirable fines. It is recommended that a maximum of 1/10 of 1 per cent be permitted to pass a 100 mesh (149 μm) screen.

The bulk density of a granular carrier is an important property because it determines both the size of a batch which may be produced in a blender of a given capacity and the size of the bag which is to be used for the container. Because the formulation of impregnated granular pesticides involves the absorption of all liquid ingredients, the volume of a given weight of formulation is the same as that of the unimpregnated carrier which it contains. Table 5 shows properties of typical granular carriers.

TABLE 5. PROPERTIES OF TYPICAL GRANULAR CARRIERS

	Bulk density (lb/ft^3)	*Relative sorptivity*	*Relative hardness*
INORGANIC			
Clays and minerals			
Attapulgite	28/36	high	high
Montmorillonite	55/65	low	high
Diatomite	20/30	high	medium
Vermiculite	8/12	high	low
ORGANIC			
Botanical			
Maize cob	22/32	medium	medium
Nut shell	35/45	low	medium

The use of solid pesticides in dust and granular formulations may cause caking depending on the concentration of the toxicant, the volume of liquid solvent and the handling conditions. Attapulgite and montmorillonite vary in their particle size and sorptivity, and these properties are critical to caking in border-line formulations. Because carriers adsorb and absorb differently, the time of pesticide distribution is critical for certain carriers.

The semi-solid pesticides such as heptachlor and aldrin have more problems with caking than the high-melting pesticides such as dieldrin and endrin. Liquid pesticides seldom cause caking on granules or dusts.

Deactivator requirements. The stability and deactivator level studies for granular pesticides are the same as those for the powdered dry formulations. Initial stability tests may be satisfactorily carried out on a small scale and at concentrations of 5 per cent active ingredient. Because it is not convenient or practical to uniformly impregnate granules in small quantities, the granular carrier may be pulverized for these tests. The quantity of deactivator required for each mineral type is nearly the same as the quantity required for dust bases and concentrates. If the quantity has been previously determined, additional experiments with the powdered granular carriers can be held to a minimum.

In formulating granular pesticides which require deactivation, every particle of the carrier must be uniformly deactivated. For pesticidal chemicals which are extremely sensitive and have an initial rate of decomposition which is more rapid than the rate of deactivation, it is necessary to deactivate the carrier prior to the spray impregnation of the active ingredient. If the deactivator is a solid, such as HMT or urea, it is dissolved in a minimum amount of water or other suitable solvent and sprayed directly onto the carrier. Alternatively, solid deactivators of this type are finely pulverized and blended with the carrier prior to spray impregnation. The spraying of a solution of a deactivator is generally preferable. Liquid deactivators are spray-impregnated directly upon the carrier with or without addition of water to attain a more uniform distribution.

If the rate of decomposition of a pesticidal chemical on a surface-active carrier is reasonably less than the rate of deactivation, the deactivator is dissolved or mixed in the concentrated spray solution to permit simultaneous deactivation and spray impregnation. Generally, this is a desirable procedure because the large volume of liquid sprayed onto the carrier increases the probability of a uniform distribution of the active ingredient and the deactivator.

Solvent selection. Spray concentrates used for the impregnation of granular carriers are normally prepared in batches at the time of formulation. Because the spray operation is carried out at any temperature from ambient room temperature up to 82° C, there are no limits to the cold-solution stability as there are for emulsifiable concentrates and oil bases. The solvent portion of a granular formulation has the following three principal functions: maintain the pesticidal ingredient in a liquid condition so it can be sprayed, provide sufficient volume for uniform distribution of the pesticide (and deactivator) upon the carrier and reduce the viscosity of the liquid or molten pesticidal ingredient for good atomization from the spray nozzle. Heat is applied to the spray liquid to maintain a temperature at which crystallization cannot occur and to reduce the viscosity for improving sprayability. The viscosity of the spray mixture at the spraying temperature preferably should be below 10 cp. Generally, the effectiveness of atomization increases as the viscosity decreases.

For economic and safety reasons, hydrocarbon solvents such as kerosene, xylene and heavy aromatic naphtha are preferred. These low-cost solvents have flash points of 27° C or higher. When hydrocarbon solvents are unsatisfactory because of poor solubility, polar solvents such as cyclohexanone, diacetone alcohol and normal propyl alcohol are used. Volatile solvents, such as methylene chloride, are used with suitable allowance for their evaporation from the formulation. The higher-boiling solvents, which evaporate more slowly, are included in the final weight of the formulation.

For the simultaneous impregnation of the deactivator and the toxicant-solvent system, all materials are combined in the spray tank, which should be heated if necessary to bring them to the proper temperature for complete solution and viscosity reduction. If the deactivator or deactivator mixture is immiscible with the toxicant spray solution, an efficient agitator in the tank keeps all material uniformly dispersed. If extremely high concentrates of pesticidal chemical and solvent are to be sprayed at elevated temperatures, all spray lines, filters, pumps and nozzles must be heated to prevent a loss of heat and possible crystallization during the spray cycle.

The position of the nozzle in the blender must place it directly in the centre of the plane of granules when the blender is in motion. The axis of the nozzle should be exactly perpendicular to this plane, and the orifice should be at a sufficient distance from the plane of granules so that maximum coverage of the surface is attained just within the outer periphery of the spray pattern hitting the walls of the blender. A spray nozzle giving a full cone pattern with a 120° spray angle is effective.

Sieving and attrition tests. A necessary condition for the spray impregnation and blending process is that the attrition of the particles to produce fines be minimal. A sieving test on both the finished product and the untreated granular carrier indicates excessive attrition; e.g. if the number of particles passing the finest screen designation of the nominal particle size increases by 5 per cent total weight of the formulation. The problem can be overcome in the following ways: select a carrier which is harder or less subject to attrition; select a carrier which is more skewed toward the larger particle size of the distribution; decrease the blending cycle; or redesign various steps in the loading, blending and discharging processes. Attrition that takes place in the handling of the granule by equipment such as a screw elevator can be substantially reduced by the use of bucket elevators or pneumatic conveyors.

Stability and storage tests. Experimental granular formulations of the chlorinated hydrocarbons should be tested for storage stability by accelerated ageing at 50° C. The samples are placed in tightly closed jars and kept at the elevated temperatures for periods up to 84 days. To begin the tests, each sample is analysed for active ingredient immediately after preparation. The samples in accelerated storage conditions are reassayed after periods of 7, 14, 28, 56 and 84 days. A maximum loss of 5 per cent active ingredient in 84 days is acceptable.

7. PESTICIDE PRODUCT QUALITY CONTROL

by Mason H. Woolford, Jr.[*]

An ideal system of pesticide quality control will be considered for a large manufacturing plant in the United States engaged in the formulation of a wide variety of pesticide products. The usual plant equipment of grinding mills, filling machines and blending equipment presents all the problems likely to be encountered in the formulation of pesticide products, e. g. cross-contamination, potency, correct formulation and packaging. No matter how small or how large the operation is, some systematic control is necessary to ensure that a uniform quality product is delivered to the consumer. This is the function of product quality control.

Pesticide quality control in the United States is a well-established concept. There are a few formulators who practise very little quality control, but most larger operators have highly developed quality-control systems. The larger the plant and the greater the production, the greater is the need for quality control. But in every formulation operation the minimum need is to verify compliance of the final product with specific standards. What are the results if the production foreman leaves out the emulsifier; if a parathion emulsifiable concentrate instead of a specified malathion product is put in the container; if glass bottles are over-filled with an organic liquid formulation which expands during warm weather and bursts the container? All of these problems can be prevented by effective quality control.

The economic importance of quality control may be seen from the size of the pesticide market. A survey[1] indicates that the production of pesticide products in the United States is growing at a rate of about 16 per cent annually. The manufacturing value of pesticide production was more than $1 billion in 1968. The estimated retail sales of these products were about $1.7 billion, including exports of about $200 million. By 1975, the retail pesticide sales are expected to be more than $3 billion.

Although the demand for the products of the pesticide chemicals industry is very great, the industry is highly competitive. Consequently, the failure to produce a uniform-quality product may result in loss of sales. The producer with a good economical system of quality control will consistently market his products.

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[1] *Chemical Week*, 12 April 1969, p. 38.

QUALITY CONTROL

Objectives and importance

The ultimate aim of quality control is to offer a product to the customer that must satisfy his requirements. It is difficult for production or laboratory personnel to know the customer's needs since very few of them have direct contact with the customer. Production and laboratory personnel must rely on information from other personnel within their own organization, for example, salesmen, agriculturalists and technical service representatives, who have close contact with customers and understand their preferences, needs and complaints. Good liaison, therefore, should be maintained among personnel in production, marketing, quality control and formulation in order to develop products that meet the specifications of each customer.

The customer can expect that the product he buys will perform according to the manufacturer's claims. The product purchased today should have the same colour, flowability characteristics and emulsifiability as the product purchased yesterday or the product to be purchased tomorrow. These product characteristics are apparent to the customer and help develop confidence that the manufacturer will provide consistently high-quality products. However, product potency, compatibility of the pesticide with the containers or other ingredients of the formulation and the expected long-term stability of the product are not apparent to the customer. Poor performance in any of these areas will probably result in the loss of customers. A sound, realistic system of product quality control is the best means for maintaining high sales.

There are many definitions of product quality and of the system for its control. The following examples are representative:

> *Quality:* "The quality of a product is its degree of possession of those characteristics designed and manufactured into it which contribute to the performance of an intended function when the product is used as directed."[2]
>
> *Quality control:* "An effective system for coordinating the quality maintenance and quality improvement efforts of the various groups in an organization so as to enable production at the most economical levels which allow full customer satisfaction."[3]

Quality must be built into the product during research, development and production. Awareness of product quality should be a guiding principle from product concept through the various stages of development to final delivery of the product to the customer.

In developing quality products and in perfecting the system which will aid in the continuing maintenance of the quality, additional costs must be considered. The criteria is to maintain a quality product in the most efficient and economical way so as to be competitive in price. Therefore, it is necessary to

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[2] *General Principles of Total Control of Quality in the Drug Industry* (1967) Quality Control Section of Pharmaceutical Manufacturers Association.

[3] Feigenbaum, A. W. (1950) *Quality Control: Principles, Practice and Administration,* McGraw-Hill, New York.

manufacture and market products of consistently high quality, which are as good or better than the competitive product.

The functional responsibility of quality control should be delegated to one individual. Moreover, the person chosen for this position should report to a sufficiently high level of management that supports a decision of disapproval of substandard product lots, even though this might cause a delay in meeting schedules. Ideally, the manager or director of quality control should be on the same level as the heads of sales and manufacturing departments. Although this ideal situation is seldom realized, the function of quality control should never be relegated to sales or manufacturing activities.

On the other hand, the quality-control function should not be permitted to become so independent as to become an end in itself and demand a degree of perfection which production cannot meet. The production department is concerned with meeting schedule deadlines, production costs and quantities and consequently often is impatient with interference from the quality-control section. On the other hand, the main task of the quality-control section is the maintenance of quality. When each department recognizes the aim of the other, a better balance of production and quality can be maintained.

The necessity for quality control should be impressed upon every employee. Consistently, high quality cannot be maintained without the proper controls. The entire organization should be indoctrinated to accept quality-control procedures as a way of life.

The management level to which the quality-control function reports should issue a written statement to all employees outlining the quality-control policy and programme.[4] This is important for the following reasons:

Quality control acts as a series of "ground rules" within which the plant quality-control programme can operate;

Quality control acts as a means of communication to inform all plant supervisors and employees about the quality-control plans and objectives of the company.

Responsibilities

An effective quality-control section should be assigned the following duties:

Develop methods of analysis for raw materials and finished products;

Develop specifications for raw materials, finished products and for packaging materials;

Check equipment design and insist upon changes when equipment has been found to cause pour quality production;

Run a continuing check on production practices and report any condition found contributing to poor product quality;

Check incoming raw materials for conformity to specification;

Check all finished batches or lots of production for conformity to specifications. With this approval, the authority is given to release for sale lots

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[4] *Ibid.*

passing all specifications and to reject all lots failing specifications with instructions to rework or destroy;
Handle customer complaints;
Inspect finished materials and proper fill of containers;
Collect representative samples for analysis.

INSPECTION

The quality-control section of a company assures the high quality of product and production. The staff should include inspectors whose functions are clearly understood. Properly trained quality-control personnel should be able to spot faults during production, such as improper fill of liquid or powder, poorly affixed labels or any action which, in their opinion, would contribute to a reduction in quality. The action should be brought to the attention of the production supervisor who should cease production until the observed deficiency is corrected. It is preferable to discover a quality problem at an early stage and not after the entire lot has passed a particular production step. Furthermore, it is unacceptable to have a quality problem discovered by the customer or a regulatory agency.

Individuals chosen for quality inspectors should be carefully screened. Quality inspection must be performed in a careful, diplomatic manner; otherwise the entire concept might be resented by the production department. Officious individuals would never perform satisfactorily in this position; tact and intelligence are desirable qualities for quality-control personnel. The following guidelines should be observed:

Sampling of raw materials and finished products should be done by trained samplers from the quality-control section and not from the production department;
Sampling procedures should be carefully developed with special attention to products needing special care;
Safety precautions should be observed in handling toxic and hazardous substances;
Samples should be representative of the batch or lot samples;
Since the approval or rejection of products depends on the sample taken, great care should be exercised in proper sampling technique with statistical significance.

CUSTOMER COMPLAINTS

Customer complaints should be forwarded to the quality-control section and handled promptly and thoroughly. Recurring complaints might indicate a serious quality defect in the product and require a major evaluation of the product that could lead to reformulation, different packaging material, change in emulsifier or other action.

There are many varieties of complaints and subsequent corrections, e.g. if the customer's problem is emulsification, a generous sample of the water he uses should be obtained for testing. If no immediate emulsification results, his mixing equipment should be examined. It may be that the customer is not using the products according to the instructions. Periodic field visits are important to observe how the material is being used. Customers may not read directions, and sometimes, the directions are too complicated and need revision. Observation of the mixing equipment in operation may suggest an idea for an improved formulation.

Whenever possible, samples should be sent to the testing laboratory in a proper container. Polyethylene bottles and caps with soluble plastic linings are unacceptable because chemical reaction between the liquid product and packaging material may obscure the formulation problem. Powder and dust should be forwarded in wide-mouthed bottles or in strong paper bags. Paper bags with a moisture barrier and resilient polyethylene bags are acceptable for this purpose.

Specifications

The quality-control section should be responsible for specifications for all raw materials, finished formulations and packaging materials. Specifications should be developed by committee action, if possible. Members of the committee should include functional representatives from sales, manufacturing and quality control. The chairman of the committee should be a representative of the quality-control director.

Specifications are the standards against which incoming raw materials are measured as well as the lots of finished products shipped to the customer. Specifications are the allowable limits within which characteristics of a product or compound may vary and still maintain acceptability of quality and performance. Failure to comply with specifications should mean rejection of the product. The specifications should be sufficiently flexible to include any variation in assay or manufacturing but not so broad as to encourage sloppy production procedures. Indeed, when possible, specifications should be tightened as production experience is gathered for a new product. If production calls for a relaxing of specifications, the production procedure should be reviewed. Perhaps improvement in the production procedure may lead to an improved product rather than one of dubious quality due to broad specifications.

Specifications must be developed for the raw materials used in formulations, the finished products and packaging materials. In most cases, the supplier of raw materials will furnish his own specifications. A reliable supplier will furnish raw materials meeting rigid specifications. In most cases, materials can be accepted on protocol from the supplier. It is prudent, however, to spot-check these materials. This is especially pertinent if the presence of a known contaminant in the raw material can cause a breakdown in the pesticide formulation. Excess acidity, alkalinity or water are often the cause of product breakdown. Occasional checks can be made on raw materials to ascertain that these contaminants do not exceed the limits of specification. Screen size of clay granulars should be checked periodically, especially in cases where a problem of dustiness in the product exists.

Dust diluents and granules should be periodically checked for the presence of foreign matter such as nails, twine from bagging operations, sticks, stones or any material likely to interfere with the operation of the customer's applicator.

No raw material should be used for manufacturing unless it passes specifications and is released by the quality-control section. A system of tagging or marking should distinguish materials released for manufacturing and those not yet tested. Materials recently received and not yet tested or passed should be stored separately from accepted or passed lots.

New sources of raw materials must be sought to assure a constant supply. Occasionally, suppliers deplete their stock, and the lack of material may cause a loss of business to the manufacturer since he will be unable to fill orders on time.

New materials, especially clay diluents and emulsifiers, should be checked for compatibility with the company's formulation. Some insecticides which are stable in technical form and liquid formulations show marked decomposition on certain of the commercial mineral carriers used in the preparation of dust and wettable powder formulations (see chapter 6). Before a new carrier is used in formulation, it should be tested by preparing a small batch and checking decomposition of the pesticide by chemical analysis (see chapter 6).

The inherent properties of the pesticide, the carrier and diluent must be known to produce formulations having both a good shelf life expectancy and satisfactory physical characteristics. The surface of some carriers tends to be catalytic due to the presence of metallic ions, metallic oxides or other surface hot-spots which contribute to breakdown of the pesticide upon prolonged storage. These detrimental effects are especially pronounced in diluted formulations of some pesticides prepared directly on highly sorptive clays and when dust concentrates are diluted. The use of deactivators may improve some carriers to the point where they are compatible with the pesticide. The deactivator for one pesticide may not work for another, however, and each deactivator must be tested for each pesticide.

New and old emulsifiers should be tested from time to time by preparing a small batch and actually checking emulsification properties. Occasionally, it is advisable to obtain an advance sample before purchase.

Specifications for solvents, in many cases, must include limits for water and acidity or alkalinity. Some organophosphates are particularly sensitive to alkaline conditions and are rapidly degraded in pH values slightly higher than neutral. For some pesticides, traces of metal cannot be tolerated. This type of information is usually supplied by manufacturers of technical pesticides. Solvents should be checked periodically for specific gravity and colour.

Specifications for the technical pesticide are generally supplied by the manufacturer on a minimum guarantee basis (e. g. not less than 95 per cent). For manufacturing purposes, it may be necessary to obtain the actual assay for the lot that is purchased. Botanicals (pyrethrin, rotenone, sabidilla, ryania and red squill) are marketed on an assay basis. Information on the formulation compatibilities and uses is generally available in a formulation handbook from the supplier.

To develop specifications for the finished formulation, the quality-control section must know the end-use of the product. An emulsifiable concentrate should form a stable emulsion under the conditions of the method of testing; water-dispersible powders should pass realistic suspendibility tests; dusts should have particle size requirements. Acidity, alkalinity, presence of water, metal, compaction, stability at elevated temperatures and a number of other variables should be considered. It is important that the physical appearance, colour and flowability do not vary from one batch to another. Prime consideration should be given to active ingredient content, which is usually expressed as per cent by weight.[5]

Specifications for pesticide content are generally based on the precision of the assay method used, variations in manufacturing and the length of over-age used to guarantee shelf life for at least one year. Batches of bulk product should be stored in a locked area until released for filling by the quality-control section after they have passed all specifications.

Specifications for packaging materials should be developed. Since moisture content is important for dusts and wettable powders, there should be a layer of material in the bag as a moisture barrier. Some calcined carriers may take up water which can be deleterious to some pesticides depending upon whether the diluent is inherently a base or an acid. Moisture uptake can dilute the product and result in a lower percentage of active ingredient. Some pesticides have an obnoxious odour and a tight seal is required, especially if the product is to be stored in an enclosed warehouse.

Polyethylene bottles may be affected by the solvent of the formulation or the formulation itself. The result is collapsed or mis-shaped bottles after several months on the shelf. The lining of caps should be unaffected by the formulation; polyethylene inserts are preferable to either rubber seals or plastic-coated cardboard.

Glass bottles and polyethylene bottles should be inspected for volume, chips, cracks or breaks. Batches of bottles from one supplier may actually be several ounces less in capacity than a lot from another supplier. Care must be exercised not to fill bottles beyond the allowable head space to avoid trouble due to expansion during storage in hot weather.

Many liquid technical pesticides and liquid formulations are unstable when packaged in metal containers due to interaction between the pesticides and metal. To maintain the stability of these containers, it may be necessary to coat the inside of steel cans with two layers of a high-baked resin properly applied and cured in accordance with the manufacturer's recommendations. Continuity of lining is essential and all fittings must be properly coated. It is advisable, of course, to conduct storage tests on individual products before adopting a specific lining for commercial use. Metal containers should be inspected for adherence to specifications for volume and particularly for leakage among 1- and 5-gal pails.

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[5] A good guide is World Health Organization (1967) *Specifications for Pesticides used in Public Health*, 3rd ed.

If the writing and printing of labels is a quality-control function, the text for labels should conform to all federal and state regulations. Instructions for use of the products should be clearly written and not subject to misunderstanding. If statements of content are necessary or a requirement, the chemical formulae must be accurate.

If labels are not a quality-conrol function, quality control should at least be responsible that the labels are correct in all details and are worded and printed according to all current regulations. Furthermore, labels placed neatly on bottles and packages contribute to the over-all attractive appearance of the packaged item.

Method of analysis or testing

Methods of analysis for the active ingredient should be available for all formulations. The methods generally supplied by the basic pesticide manufacturer are available on request. The methods of analysis of concentration in the common formulations of widely distributed pesticides are readily available, e. g. the specifications of WHO or any similar collection (see chapter 4). These methods are usually recognized as official and are generally simple and free from interference from other components of the formulation. The results are reproducible and usually representative of the actual concentration of the pesticides even after considerable degradation as a result of its age, improper storage conditions or other factors contributing to the decomposition of the active ingredient. The analytical methods are generally used by government regulatory officials, and the results can be used in court action by a plaintiff against the company.

Standard methods of analysis for all other tests to be performed can usually be obtained from various recognized collections of methods. The methods include specific gravity, specific rotation, index of refraction, emulsification, apparent density (for dusts and granulars), colour, pH, particle size, dispersibility, acidity (as sulphuric acid) or alkalinity (as sodium hydroxide). The quality-contol section may perform other tests developed in its own laboratory. These tests should be reproducible under a variety of conditions to be encountered in different laboratories. For example, a test might be a method to measure frothing (an undesirable characteristic) for a water dispersible powder to be dispensed from a field spray tank.

In a plant producing a number of liquid formulations, identity tests are an absolute necessity. One should not rely upon odour, taste or physical handling; these techniques may be dangerous and result in injury to personnel or incorrect labelling of formulations. If the basic suppliers cannot furnish identity tests, the ingenuity of a control chemist can be put to work. Currently, thin-layer chromatography is often used. Most emulsifiable concentrates appear similar but may vary widely in toxicity. The same is true for dusts, wettable powders and granulars if a variety of them are produced in the same plant.

For each raw material, technical pesticide, finished formulation and packaged item, a file should be kept containing specifications, methods of analysis and records of analytical results. Specifications should be reviewed periodically and changed whenever necessary. Methods of analysis should be changed when improvements are developed. A specification change does not necessarily mean a method change. Sometimes change in a method may require a change in specification if the new method is more accurate or precise. Specifications should be as tight as allowed by production, the analytical method and the stability of the product. The goal should always be the production of a product consistent in appearance, performance and customer appeal. Realistic and soundly conceived specifications are very helpful in the achievement of this goal.

Stability

Formulations of pesticides should be stable during the time they are expected to be used by the customer.[6] Products intended for agricultural use are prepared well in advance of the growing season for delivery to the customer when needed. Sometimes, stock will be carried over through the following year; therefore, the formulation should contain the active ingredient at label strength for at least 1.5 years after manufacture. Certain technical pesticides are quite stable by themselves, but under other conditions they will degrade quite rapidly. Some organophosphates, for instance, hydrolyze quite readily even under mildly alkaline conditions, yet they are very stable on the acid side. Emulsifiers can degrade or react with a formulation ingredient, so as time passes, the product's ability to emulsify may decrease. In the formulation of pesticides, knowledge of the active ingredient is absolutely essential. This is generally obtained from the original supplier, who knows most of the conditions under which the product is stable. The supplier's data include compatibilities, storage conditions, proper packaging materials, solubilities and the general, chemical and physical properties which can provide essential information for the formulator.

In most cases, the original supplier does not know all of the conditions under which a product may be used. He probably has not determined the stability of the product with all of the emulsifiers, conditioners, stickers, spreading agents and carriers which are available. A formulator may develop combinations never envisioned by the manufacturer of the product. If this is the case, the formulator should conduct stability studies on the standard formulations before changing to an emulsifier or carrier with which he has had no previous experience.

Liquid formulations should be tested periodically for a minimum of 12 months at room temperature (25° C), for nine months at 37° C and for two months at 45° C. These formulations should be tested for potency of active ingredients, emulsification and for appearance (formation of sludge, separation, change in colour and formation of odour). Powder or dust formulations and granulars should be tested using the same time periods and temperatures as above for potency of active ingredients, suspendibility, wetting and caking. From the stability study, the amount of over-age of the active ingredient necessary to maintain label strength for the specified period is known.

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[6] See also chapter 6.

Solvents are generally well standardized; a grade of solvent from one supplier is much the same as from another. Specifications vary little. If one solvent is substituted for another, such as cyclohexane for toluene, differences may be found in solubility, compatibility and emulsification. A stability study should be run on a sample prepared with the new solvent.

In order to follow the quality of the products in the field, representative samples of complete packages should be taken from the sample line during the filling operation. Samples should be taken from several lots during the year in this manner, stored at ambient temperature and inspected periodically over a period of not less than two years. In this way, information can be obtained which may possibly forestall customer complaints. At least, product-quality problems can be recognized and solved before they become serious.

Federal and state regulations

In the United States, any product in commercial channels may be sampled and tested by the USDA and by officials of the state in which the product is sold. The sample will be assayed and if found deficient, the particular lot of formulated material may be removed from the market. This can prove very embarrassing to the company because reports of these actions are generally published.

In order to ship pesticide products manufactured in one state for sale in another state, the product must be registered with the USDA, which samples products in interstate commerce. In addition to the assay, the registration of the product and the conformity of the label to the official registration by the company are checked.

Provisions for registration and sale are clearly detailed in the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) approved 25 June 1947. Penalties for violations of FIFRA can be relatively severe and include fines and imprisonment or both.

All products are expected to meet label guarantee. The methods of examination of samples are those adopted and published by the Association of Official Agricultural Chemists where applicable. Other methods may be necessary to determine if the product complies with the law.

If from an examination or analysis, a product appears to be in violation of FIFRA, a written notice is sent to the person against whom criminal proceedings are contemplated to give him an opportunity to offer a written explanation. The notice states the manner in which the sample fails to meet the requirements of FIFRA and the regulations.

> "Shippers or other claimants of the product will be given an opportunity in pending court actions to defend against USDA charges.
>
> "Federal pesticide regulations are designed to protect the public from possible injury to humans or animals or financial loss from mishandled, adulterated or ineffective products."[7]

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[7] United States Department of Agriculture release No. 2366-68, 23 July 1968.

Products in interstate commerce showing poor stability will almost certainly be in violation of the law. An alert quality-control section should be able to prevent the release for sale of any product failing to meet the regulations of any state or of the USDA.

Cross-contamination

During the past few years, the very serious problem of cross-contamination or the presence of one pesticide in the formulation of another has become evident in the pesticide industry. It has resulted in such incidents as finding illegal residues of chlorinated hydrocarbons in eggs. An investigation showed that the cause was not contaminated feed or the improper use of insecticides but that certain pesticides approved for use in poultry houses contained others that were not approved. Presence of an herbicide in an insecticide formulated for use on an agricultural crop can be damaging to the point of complete loss of the crop.

The extent of cross-contamination was not discovered until the advent of new analytical techniques and instruments. Up to that time, many formulators were entirely unaware of this condition until analyses of samples by several of the states were brought to their attention.

Now that the problem is recognized, means of prevention are being devised. The principal method of prevention is the thorough cleaning of equipment just after preparation of a pesticide formulation. Good housekeeping is the basic essential to prevent cross-contamination by keeping plant and operating lines clean and orderly. Scheduling of production is important, and adequate testing must be performed to show the complete removal from the equipment of the previous formulation.

It is generally agreed that the design of most grinding, blending and mixing equipment makes it difficult to do an effective job of cleaning quickly at a reasonable cost. Many formulating plants were custom-built and need considerable redesigning to institute an adequate quality-control programme for current requirements.

The development and promulgation of a code of good manufacturing practices could be undertaken. This has been done by the FDA for the drug industry and for medicated pre-mixes intended as animal feeds.

The National Agricultural Chemicals Association (NACA) has studied cross-contamination. By committee action, the NACA has suggested allowable limits of cross-contamination of one pesticide in another based upon the specific pesticide and end-use of the product. The following highlights are from the cross-contamination committee report of the NACA.[8]

In the preparation of liquid pesticide formulations, great care must be taken to eliminate traces of the preceding formulation from all mixing equipment and filling apparatus. This will be done by the use of solvent rinses. The amount

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[8] *Manual for Prevention of Cross-Contamination of Pesticide Chemicals* (1965) National Agricultural Chemicals Association, Subcommittee on Cross-Contamination of the Grady Committee, Washington, D.C.

of solvent required for each rinse will vary with the size of the equipment, the type of product and the solvent used.

From 20 to 50 gal of solvent are generally sufficient to allow continuous recirculation of the rinse in most types of equipment. Each rinse should be recirculated for 3 to 5 minutes throughout the entire manufacturing and drumming system for the solvent to wash and dissolve all possible contaminants. All strainers in the system should be removed and cleaned. Filters should be cleaned and the residues from the filters destroyed or deposited in suitable disposal locations.

The number of rinses required to free the system of any contaminants may vary from one to five but can only be determined accurately by chemical analysis. If the solvent used for rinsing is the same material that is used to manufacture the product, the rinsings may be carefully saved, labelled and stored for use as a solvent the next time the same product is produced.

It is most important to be certain that the sample obtained for contamination analysis is representative of the finished material. Therefore, samples must be taken from the packaging point and not the mixing tank.

For the granular formulations, particular emphasis should be placed on the importance of proper cleaning of the interior of tumbler-type mixers due to the affinity of the impregnated particles for the interior of the tumbler. Cleaning with mechanical equipment may be required. In other cases, steam cleaning or hot-water washing may be recommended. Visual inspection should determine the effectiveness of cleaning procedures.

It is necessary to study each blending unit to determine the amount of material that is retained in the equipment after a batch has been emptied prior to cleaning. Cleaning procedures can be established as adequate only after a thorough investigation of existing equipment and practices.

Currently, increasing attention is being paid to the problem of cross-contamination. The analysis for the presence of one pesticide in the parts per million range in the formulation of another pesticide is very often a job that requires the ingenuity of the analytical development chemist (see chapter 4). For example, a 50 per cent emulsifiable concentrate contains 50 parts by weight of the technical pesticide. This product itself may be only guaranteed 90 per cent pure. The resultant emulsifiable concentrate is composed of 45 per cent by weight of the pesticide, an additional 5 per cent for the emulsifier and the balance as solvent. The 5 per cent of this formulation from the technical product itself is probably of completely unknown composition and contains one or more components which may behave analytically in a similar manner as the contaminant sought.

To compensate for this unknown quantity, a sample of the formulation is prepared in the laboratory from the same ingredients contained in the finished batch. Care is taken to ensure that this mixture contains the identical lot of technical pesticides. In this way, the contaminant may be spotted with relative ease, or another analytical method must be developed.

The limits of contamination suggested by the NACA are very helpful to the quality-control analyst. It is more economic to state that a contaminant is present at a concentration of 500 ppm rather than 100 ppm.

In the present state of the art, some of these analytical problems are insoluble in the time allotted to them from a financial viewpoint. With the recognition of the problem, however, good manufacturing practices and an alert quality-control section can minimize the seriousness and frequency of cross-contamination.

The laboratory

Each quality-control system should have an adequate analytical laboratory. In some companies, the head of the laboratory is the manager of quality control. In others, the laboratory is only one aspect of a sophisticated system including a product-security section, sampling section, and records and files, that all report to the quality-control manager.

The laboratory can range from a simple organization composed of several technicians performing the physical tests of screen testing and emulsification (excluding chemical assays for active ingredients) to a staff of several professional chemists developing methods, assaying all finished formulations, checking all materials against specifications and testing for cross-contamination.

Regardless of the size and scope of the laboratory, a retention sample in addition to a sample for analysis should be taken of each raw material (including technical pesticide) used in the formulation and of each lot or batch of formulation manufactured.

The size of the sample should be at least three times the quantity needed for a complete quality-control check. The container should be of amber glass with a cap having a polyethylene insert. The cap used for solid substances need not be this type but should be capable of maintaining an airtight seal.

The samples taken for analysis should be stored in a locked room preferably without windows; the temperature should be maintained constantly between about 20° to 30° C. Samples should be stored for at least 2 to 3 years. All sampling for testing and retention, except for the sampling of the complete package, should be done by quality control. Complete package sampling includes the label and container and may be performed by production during the filling operation.

The purpose of a retention sample is to serve for ready reference in case of complaints since the cause of the complaint may be traced to one ingredient of the formulation. A retention sample file may be a government requirement.

All analytical work on samples received in the laboratory should be recorded. State or federal government regulations may require that notebooks of analytical work be maintained and signed by the person performing the work and that these records be available for inspection.

Laboratory personnel should obey safety regulations and be aware of the toxic nature of many of the materials with which they will be working. Safety glasses should be worn, and hazardous work (work involving flammable solvents or giving rise to noxious gases) should be performed in a fume hood (see chapter 8). There should be no eating, drinking of beverages or smoking in the laboratory. These are all common sense rules, and good supervision should be exercised to see that these rules are not violated.

At least one graduate chemist should be among the laboratory personnel, who may be the head of the laboratory or the supervisor directly under the laboratory manager. Many of the tests, such as screening and specific gravity, can be performed by technicians after some training, since most of these tests are routine, but interpretation of results must be the responsibility of a professional chemist.

Some formulation plants may not be able to perform all of the necessary tests at the plant. One of the reasons may be that the only method available for the assay of the active ingredient requires an analytical instrument not available at the plant. In this case, it will be necessary to send the samples to a commercial laboratory specializing in quality control.

The recent technique of gas-liquid chromatography (GLC) is used by many technical pesticide manufacturers (see chapter 6). Among its advantages are specificity, rapidity and ease of assay. Due to highly sensitive detectors, less handling of the sample is required because interferences normally encountered in other methods, such as infra-red or ultra-violet spectroscopy, are kept at a minimum. The GLC method, therefore, lends itself to analysis of many samples daily. Another advantage of the method is the relatively low cost of many available instrument models. The analytical apparatus of one very large custom formulator consists of only a balance and a gas chromatograph.

Thin-layer chromatography is another procedure extremely simple to operate. This technique is used for identity testing and for cross-contamination. Both gas-liquid chromatography and thin-layer chromatography can be performed by technicians after a relatively short period of training. With these two procedures and a modest capital outlay, a large part of the analytical work of quality control of a pesticide formulation plant can be performed.

8. SAFETY PROBLEMS RELATED TO EXPOSURE OF WORKERS IN PESTICIDE FORMULATION PLANTS

*by Homer R. Wolfe**

Workers in pesticide formulation plants are often exposed to relatively high levels of pesticide compounds. Since most chemical pesticides have at least some degree of toxicity to man, it is important that all workers, as well as management, be aware of any potential hazard that may accompany exposure to such compounds. Experience has shown that if proper precautionary measures are observed, workers can safely handle even the more toxic compounds. Although pesticides cause illnesses and even deaths each year, many of these cases are a result of carelessness or accident. Proper education as well as close supervision of workers may prevent some accidents and greatly reduce the number of illnesses resulting from carelessness.

The main purpose of this chapter is to discuss some of the problems related to exposure of workers in formulation plants, to indicate various ways that unnecessary exposure to pesticides may occur and to point out certain precautions to prevent such exposure. Discussions of medical supervision, clinical aspects of poisoning, antidotes, the effect of pesticides on the body and steps to take in case of poisoning are given in chapter 10.

EDUCATION OF EMPLOYEES

It is essential that all employees, regardless of their duties, have at least some knowledge of pesticides. Well-informed personnel are more likely to take proper precautionary measures when handling toxic materials and thus help to maintain a good safety record for the formulation plant. The personnel should be informed about the different classes of pesticides, i. e. chlorinated hydrocarbon, organophosphate, carbamate etc., and their relative toxicity. Pesticide workers should be aware that pesticides may enter the body by more than one route, and that these routes of entry must be protected in order to avoid excessive absorption of pesticides. One or more persons should be trained in first aid and be competent in the proper application of artificial respiration. The consulting physician may advise that workers be given enough information about some of the more characteristic signs of poisoning so that they will recognize them and report to the supervisor.

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MEDICAL SUPERVISION

Regardless of the size of the plant operation, it is wise to arrange some type of medical supervision. This is particularly important if highly toxic chemicals are being formulated. Regular employees should be given a physical examination at least once a year. A pre-employment physical examination should include a blood cholinesterase test for employees who may work with the more toxic cholinesterase-inhibiting compounds. This test will provide some indication of the normal cholinesterase activity level and may be useful later in determining whether an illness is due to pesticide poisoning. Personnel working with such compounds, especially the highly toxic organophosphate pesticides, should have their cholinesterase activity checked at regular intervals in order to detect any appreciable deviation from normal which may indicate impending danger of poisoning. If significant reduction in cholinesterase activity is noted, the employee should be removed from the work situation, which might be a source of exposure to pesticides, until the worker is advised by a physician that it is safe to resume his regular duties.

SELECTION OF WORKERS

Risk of injury or illness should be minimized by using the best informed and most careful employees in work situations that are potentially the most hazardous. Unfortunately, this principle is not always observed. The more hazardous jobs are usually dirtier, require more physical effort and thus are less desirable than other positions in a formulation plant. As a consequence, new, inexperienced personnel are often given the more hazardous jobs, while those with more seniority and knowledge of pesticide safety move to the more desirable positions.

Careless workers are not particularly difficult to detect. Some fairly close observations of their work activities quickly reveal this tendency. For example, careless operation of equipment such as the bagging machine may soon cause an excess of dry pesticide formulation in the air and around the formulating machinery even though relatively efficient ventilation equipment is in operation. Such excess dust in the air may settle to form a layer of contamination on clothing, equipment, warehouse structural components and flooring.

Employees should not be allowed to work alone when handling hazardous pesticides. In some plants a "buddy system" is practised whereby each worker is assigned a partner who is required to know at all times where the other worker is located in the work area.

PLANT VENTILATION AND SAFE USE OF EQUIPMENT

In the formulation plant, it is important that the ventilating system be maintained under negative atmospheric pressure so that any leakage will result in inflow of air, thus reducing the contamination of the work environment.

Where there is lack of adequate supervision, workers often neglect to report malfunctioning ventilation equipment; they may fail to use exhaust fans, and they sometimes open doors that allow gusty winds from outside the building to blow contamination throughout the plant.

Considerable care must be exercised when operating equipment for moving large drums of liquid emulsifiable concentrate pesticides. When a single worker tries to handle the drums, he runs a greater risk of dropping the drum or spilling the concentrate. Therefore, to avoid accidents, two persons should be assigned the job of moving heavy drums of pesticides.

In mixing liquid formulations, the use of a closed system reduces the workers' chance of exposure. During filling of containers, however, there is some chance of exposure if protective gear is not worn.

Filler spouts and nozzle mechanisms for dry pesticide packaging must be kept in good working condition to prevent excess exposure of the worker. If the auger or other feeder mechanism in the filler spout assembly malfunctions, there is a large risk of a heavy exhaust of dry pesticide at a time when the bag may not be in place. In one recorded case, the filler mechanism of a 50-lb size bagging machine nozzle was accidentally pushed, so that 1 per cent TEPP dust was blown out with considerable force. The workers near the bagging station were engulfed with the highly toxic material, and about 50 lb of the material accumulated on the floor around the bagging station. Fortunately, the workers were wearing goggles, tight-fitting respirators and other protective clothing. The machine had malfunctioned several times prior to the incident but no effort had been made to correct the situation until the more serious incident occurred.

Containers can be punctured because of careless operation of fork-lift trucks used in formulation plants to move pallets loaded with bags or cartons of pesticide. The relatively sharp ends of the fork can easily tear a bag or rupture a drum. This may result in leakage during storage and transportation. Contents of dented drums or punctured bags should be placed in new undamaged containers before shipment from the formulation plant.

GOOD HOUSEKEEPING

Good housekeeping is essential if environmental exposures are to be kept at a minimum. All spillages should be cleaned up at once. Liquid spillages should be picked up with absorbent material. In the plant, some form of dry inert material should be kept on hand for this purpose. Fine sawdust, attaclay or other fine inert absorbent material are effective.

Large quantities of dry pesticides can be picked up with a broom and dustpan. Sweepings should be placed in a special container labelled as "waste pesticidal material". A product-labelled container should never be used as a waste pesticide container. Lighter accumulations of dry pesticides on floors or other surfaces can be picked up with an industrial vacuum cleaner. An extremely smooth concrete floor is much easier to clean than one that has not been carefully finished or one that is made of wood. Thus, during construction of a formulation plant it is advisable to expend the extra effort needed to produce a very smooth floor finish. Smooth floor surfaces can be kept clean by using chemically treated dust mops with a sweeping compound.

PROTECTIVE CLOTHING AND DEVICES

Protective clothing and devices should be worn and used during all work with pesticides in order to protect the routes of entry into the body. The four routes of entry are dermal, respiratory, oral and direct entry into the blood stream through cuts or abrasions.

The dermal route is probably the one that is often overlooked by workers. Most persons are aware of the danger of inhaling or swallowing insecticides but the possibility of absorbing appreciable amounts of poison through intact skin is not as familiar. Yet this route has probably been responsible for a great many poisonings, especially from the organophosphate compounds. Dermal exposure is particulary important where liquid concentrate compounds are involved. The main body area can best be protected dermally by the use of water-repellent clothing; however, in most formulation plants the usual attire is cotton coveralls and a waterproof apron. The waterproof apron is especially needed by the worker at the bagging or mixing stations, as there is often considerable contamination on the front of his clothing. Even when the waterproof apron is used, it is very important that the worker change to freshly laundered clothing each day. A common fault in many plants is inadequate protective gear for the head. Head coverings or caps are often made of material that is easily penetrated by toxic pesticide. Certain heavy exposure situations may require goggles or a face shield to protect the eyes and face. Rubberized boots are essential in formulation plants. The legs of coveralls should be worn outside the boot tops to prevent dry pesticide from sifting into the footwear.

Hands should be protected by use of unlined gauntlet-type natural rubber gloves. The gaunlets protect the wrist area not normally covered by the sleeves and, since they have no cloth lining, they are also easier to clean on the inside. Heavyweight gloves, although durable, do not allow adequate freedom of movement or finger flexibility; furthermore, they are difficult to turn inside-out for proper cleaning. On the other hand, some lightweight gloves, although flexible enough to allow freedom of finger movement, wear out rapidly and are easily torn. Therefore, it is advisable to secure gloves of a durable quality but light enough to be easily turned inside-out for daily cleaning.

The respiratory route of exposure should be protected by a respirator capable of filtering out the compound in question. The filter cartridges should be changed after 8 hours of appreciable exposure and more often if pesticide odour is detected through the mask. If the filter pads are separate, removable items, they should be changed twice a day or more often if filter clogging causes difficulty in breathing. Gas masks with canister-type filters should be used when high concentrations of highly toxic vapours are present or when the worker is subjected to prolonged exposure in confined spaces. Use of a self-contained air supply respirator is advisable when working inside blender tanks or dust hoppers during cleaning or repair operations.

To be effective, the respirator should fit tightly enough against the face to prevent leakage. After a period of use, the cartridges and filters should be removed and the facepiece washed with soap and water. After drying, the cartridges and filters should be replaced and the proper position of the seals or gaskets should be checked. The respirator should be stored in a container in a dry place. A respirator should never be hung by the straps over a nail on a wall for storage. If it is hung by the headbands they may stretch and lose elasticity, so that it is difficult to get an airtight seal with the face the next time the respirator is worn.[1]

Personal hygiene

Even though the employer may provide a relatively safe working environment, the formulation plant worker should make an effort to protect himself from excess absorption of pesticides through good personal hygiene practices. Upon arrival at work, the worker should remove his street clothing and put on clean work clothing. No street clothing should be worn under work clothing. At the end of his work shift he should remove the clothing and place them in a bin to be laundered. He should then bathe in a shower using plenty of soap to thoroughly cleanse any pesticide from the skin before dressing in his street clothing to go home. If a worker should become excessively contaminated at any time with either a dry or liquid concentrate pesticide, he should immediately stop work, bathe and change into clean work clothing before resuming his duties. This is especially important if he has been working with the more toxic organophosphate compounds. In such a case the worker should be observed for poisoning symptoms. In most plants, the employer furnishes freshly laundered protective clothing daily.

The worker should be responsible for daily cleaning of waterproof protective clothing such as aprons, boots and gloves. It is especially important that rubber gloves be thoroughly cleaned on the inside as well as the outside. He should inspect his gloves regularly for small holes or tears and destroy those that are found to be defective.

Workers should never smoke, chew tobacco or gum, drink or eat while working with pesticides. These activities should take place away from the pesticide formulation area preferably in a separate room provided for that purpose. The hands and face should be washed before eating, drinking or smoking.

Measurement of exposure

If there is any question about the degree of exposure in different work situations in the formulation plant, both indirect and direct methods of measure-

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[1] Protective clothing when worn in hot climates may prove extremely uncomfortable to the workers, and special incentive pay may be necessary to maintain strict adherence to personnel protection regulations.

ment are available. An example of an indirect method of measurement that correlates quite well with the clinical effect is the determination of cholinesterase activity in the blood of workers exposed to organophosphate compounds. Determination of urinary metabolites excreted following exposure is another example of indirect measurement of exposure. The level of excretion of p-nitrophenol in the urine of persons exposed to parathion and the level of dichlorodiphenylacetic acid in the urine following exposure to DDT have been useful tools to determine the level of exposure in a particular work situation.

Because many pesticides are not cholinesterase-depleting compounds and because urinary metabolites for many compounds are not known, direct methods may be needed for measuring potential exposure. Potential dermal contamination can be measured by swabbing skin areas or by attaching special absorbent pads to different parts of the body or clothing of workers. Contamination of the hands can be measured by rinsing them with a suitable solvent into a polyethylene bag. The amount of pesticide found on the dermal pads, swabs or bag rinses will indicate the amount of pesticides that may have accumulated on exposed skin areas during a specific period of work activity. Respiratory exposure can be estimated from the contamination of filter pads held in special single- or double-unit respirators, from air concentration values determined by use of impinger-type air samplers or both. Chemical analysis of respirator pads or of air samples taken near the breathing zone of workers yields values that can be used to calculate the potential respiratory exposure.

DISPOSAL OF WASTE PESTICIDES AND EMPTY CONTAINERS

A problem that can be a serious hazard to the public is the improper disposal of waste pesticides that have accumulated in formulation plants from spillages, floor sweepings etc. Pesticides should never be washed into a drain or flushed into a sewage system. The best method of disposal is burial under at least 18 inches (45 cm) of soil in a location carefully selected to ensure that no surface or subsurface water will become contaminated. Adding lime or lye (sodium hydroxide) is sometimes recommended to hasten the degradation of certain compounds. However, this method is not completely reliable to make the buried material completely non-toxic. Neutralizing the poisonous effects of most pesticides is not easy, especially where large quantities of the toxic material are involved. Burning large quantities of pesticide wastes is not advisable because of possible air pollution. Even use of especially built incinerators where very high temperatures produce relatively complete combustion does not assure that no toxic smoke or vapour will be emitted.

The disposal of empty pesticide containers should not create a hazard for humans or animals. Combustible containers, such as paper bags and cartons, can be destroyed by burning; however, in some areas there is an objection to this practice because of the creation of air pollution. If such containers are burned, extreme caution should be used, and smoke should be avoided. In the United States, formulation plants usually have incinerators for burning combustible containers. Such incinerators should be enclosed by a high fence with a padlocked gate to keep out unauthorized persons. If combustible containers are not burned they should be buried.

Disposal of metal drums presents a greater problem. The drums should be returned to the manufacturing plant, but if this is not possible they should be thoroughly drained and rinsed with a decontamination solution. The National Agricultural Chemical Association of the United States has published the following procedure for rinsing different size drums which had contained organophosphate pesticides:

> For the 5-gal size, use 2 quarts of water, 2 tablespoons of detergent and $\frac{1}{4}$ cup of lye. For the 15-gal size, use 1.5 gal of water, $\frac{1}{4}$ cup of detergent and $\frac{1}{2}$ lb of lye. For the 30-gal drum, use 3 gal of water, $\frac{1}{2}$ cup of detergent and 1 lb of lye. For the 55-gal drum, use 5 gal of water, 1 cup of detergent and 2 lb of lye.
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> Carefully add the rinse solution to the drum and then rotate the container to completely wet all inner surfaces. Let the container stand at least 15 minutes with occasional agitation. Remove all bungs or stoppers and drain the rinse into an area where there is no chance of runoff into water supplies. Next, thoroughly flush both the inside and outside of the container with clean water.

Although the procedure may not completely detoxify or remove absolutely all pesticide from drums, it should render them much safer than if no rinse were used.

After the decontamination rinse, the bottoms of the drums should be punctured and the drums should be buried in a safe location as described above for combustible containers. Drums should not be allowed to accumulate in an area accessible to unauthorized persons who may be tempted to use them for trash-burning containers, livestock water troughs, storage cans or other purposes.

Decontamination of containers which have held other types of pesticides, including chlorinated hydrocarbon and carbamate compounds, requires more rigorous treatment than that described above. The manufacturing plant should be consulted for specific procedure to decontaminate drums that contained such compounds.

SUMMARY

Workers in pesticide formulation and production plants are often exposed to relatively high levels of pesticide compounds; therefore, it is important that all workers, as well as management, be aware of any potential hazard that may accompany exposure to such compounds. Personnel should know the precautionary measures that must be taken when working with different compounds, the routes of entry of pesticides into the body and how to protect these routes. Regardless of the size of the plant operation, some type of medical supervision of employees is desirable. Risk of injury or illness can be minimized by using the best informed and careful employees in work situations that are potentially the most hazardous. Care should be used in operation of equipment in order to avoid unnecessary contamination of the working environment. Protective clothing and devices should be used and be properly maintained. Good personal hygiene practices should be encouraged in order to reduce absorption of pesticides. Both direct and indirect methods of measurement of exposure in different work situations are available for certain compounds. Care should be employed in disposing of waste pesticides and empty containers.

GENERAL REFERENCES

AMERICAN PUBLIC HEALTH ASSOCIATION (1967) *Safe Practices in the Manufacture, Formulation, and Packaging of Pesticides*, New York.

CUETO, C., A. G. BARNES AND A. M. MATTSON (1956) *Journal of Agricultural and Food Chemistry*, Vol. 4, p. 943.

DURHAM, W. F. AND H. R. WOLFE (1962) *Bulletin of the World Health Organization*, Vol. 26, p. 75; (1963) Vol. 29, p. 279.

ELLIOT, J. W., K. C. WALKER, A. E. PENICK AND W. F. DURHAM (1960) *Journal of Agricultural and Food Chemistry*, Vol. 8, p. 111.

NATIONAL AGRICULTURAL CHEMICALS ASSOCIATION (1965) *Manual for Decontamination and Disposal of Empty Pesticide Containers*, Washington, D.C.

NATIONAL AGRICULTURAL CHEMICALS ASSOCIATION (1965) *Manual on Waste Disposal*, Washington, D.C.

UNITED STATES DEPARTMENT OF AGRICULTURE, AGRICULTURAL RESEARCH SECTION (1964) *Safe Disposal of Empty Pesticide Containers and Surplus Pesticides*, U.S. Government Printing Office, Washington, D.C.

WOLFE, H. R. (1967) "Safety precautions related to pesticide use", in *Proceedings of the Agricultural Chemical Application Short Course*, Yakima, Washington, pp. 11-A-29—11-A-36.

YEOMANS, A. H., R. A. FULTON, F. F. SMITH AND R. L. BUSBEY (1967) "Respiratory devices for protection against certain pesticides", *United States Department of Agriculture Bulletin*, ARS 33-76-2, revised.

9. SAFETY PROBLEMS RELATED TO TRANSPORTATION AND STORAGE OF TOXIC PESTICIDES

*by Homer R. Wolfe**

Anyone involved in the industrial production of pesticides should have some knowledge about the potential hazards during transportation and storage of toxic chemicals. There has been increasing concern about health problems arising from spillage of toxic pesticides on loading docks, in storage warehouses, ships, lorries, railway cars and other conveyances. Therefore, it is important that every effort be made to ensure safe transportation and storage of the compounds until their delivery to the consumer.

A number of incidents which have occurred during recent years point out the seriousness of this problem (see chapter 1). In the Middle East during 1967, two separate incidents of endrin leakage onto sacks of flour in the holds of ships resulted in a total of 26 deaths and more than 800 illnesses in persons who ate bread made from contaminated flour.[1] In Mexico in 1967, sugar and flour contaminated with parathion caused 16 deaths and many illnesses;[2] in Colombia during the same year, 63 persons died and 165 became ill from eating food made with flour contaminated with parathion during transportation by lorry.[3] In Canada two children were seriously poisoned by sleeping in flannelette sheets that had become contaminated with parathion in the hold of a transatlantic ship.[4]

In the United States there have been a number of spillage incidents. One of the more serious spillages resulted in contamination of a bundle of cotton trousers with the highly toxic organophosphate compound mevinphos. The trousers had been shipped in the same lorry as the pesticides.[5] Six children became poisoned

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[1] Weeks, D. E. (1967) *Bulletin of the World Health Organization*, Vol. 37, p. 499.

[2] Márquez Mayaudon, E., A. Fujigaki Lechuga, C. A. Moguel and B. Aranda Reyes (1968) *Salud Pública de Mexico*, Vol. 10, Nr. 3, p. 293.

[3] Gomez Ulloa, M., P. F. Velasco, H. Laverde de Fandino and M. E. Guerrero (1968) "Epidemiological investigation of the food poisoning which occurred in the municipality of Chiquinquira, Colombia, a preliminary report", Ministry of Public Health, Bogotá, Colombia, translated and printed by the Bureau of Occupational Health, State of California, Department of Public Health.

[4] Anderson, L. S., D. L. Warner, J. E. Parker, N. Bluman and B. D. Page (1965) *Canadian Medical Association Journal*, Vol. 92, p. 809.

[5] Warren, M. C., J. P. Conrad, J. J. Bocian and M. Hayes (1963) *Journal of the American Medical Association*, Vol. 184, p. 266.

through wearing the trousers before investigators located the entire consignment and withdrew it from the market. In Texas during 1968, six members of a family became seriously poisoned when they ate tortillas made from flour contaminated with the organophosphate compound carbophenothion.[6] The flour had been purchased in an unlabelled 100-lb paper bag from a railway salvage store. Flour samples from the family bin contained 3,220 ppm of the pesticide. In another incident oxygen respirators became contaminated with the chlorinated hydrocarbon pesticide endosulfan.[7] The pesticide and the respirators were being transported on the same truck. Containers of the pesticide broke, and the pesticide dust entered the uncovered ends of respirator tubes. The firms involved voluntarily corrected the problem. Another incident involved contamination of biscuits by the organophosphate compound azinphosmethyl.[8] Contamination occurred when bags of the pesticide were loaded on a lorry beside the biscuits. Pesticide dust migrated to the food packages. A shipment of 150 cases of biscuits had to be destroyed.

The provision of information on the toxicity and hazard of pesticides, as well as safety rules for their storage and transportation, is important in minimizing accidents. Furthermore, guidelines are given to those involved in clean-up operations after an accident has occurred.

The United States Department of Transportation has domestic shipping regulations in effect which are designed to prevent contamination through leakage.[9] These regulations require that any such poisonous materials (Class B poisonous liquids or solids) must not be transported in the same vehicle as any foodstuffs, feeds or other material intended for consumption by humans or animals unless the items are packaged in air-tight, non-permeable containers. Any vehicle used to transport such poisons must be inspected for contamination before reuse; in instances where leakage or spillage has occurred, the shipper of the material must be immediately notified for instructions concerning the best method to be employed for removal of the contamination. Any vehicle found to be contaminated must not be returned to service until the contamination has been removed. The last statement excludes vehicles used solely for transporting such poisonous materials.

Even though these regulations are in force, spillage accidents continue to occur. The importance of reporting such incidents cannot be stressed too often.

HANDLING OF PESTICIDE SPILLAGE

When an accident occurs, the primary requirement is an evaluation of the toxic hazard of the pesticides involved. Some pesticide chemicals have a relatively

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[6] Hatcher, R., M. S. Dickerson and J. E. Peavy (1968) United States Public Health Service, National Communicable Disease Center, *Morbidity and mortality Weekly Report*, 5 October, p. 376.

[7] *United States Food and Drug Administration Papers* (1968) Vol. 2, No. 4, p. 31.

[8] Stringer, J. G. (1968) *United States Food and Drug Administration Papers*, Vol. 2, No. 4, p. 4.

[9] "Hazardous materials regulations of the Department of Transportation" (1967) *Federal Register*, Vol. 32, No. 251, p. 20982.

low degree of toxicity and it would be difficult to envision any circumstances in which workers or bystanders could absorb sufficiently large quantities to produce poisoning. However, other pesticides, particularly certain organophosphate compounds, are extremely toxic and even very small quantities which could easily be absorbed by transportation workers, police, clean-up crews or even bystanders have produced poisoning. Knowledgeable evaluation of the toxic potential of the pesticide involved in a spillage accident is important to prevent possible poisoning from the more toxic materials and to minimize unnecessary precautions and concern if the chemicals involved are of low toxicity.

For this reason, spillage clean-up and safe disposal of toxic materials require personnel who have special knowledge of pesticides and chemical safety and who have proper equipment and sources of technical information available when an emergency arises. When a contamination incident occurs, it is possible that personnel from the pesticide manufacturing plant who have specialized knowledge of the toxicity and safety aspects of the specific chemicals involved may be called for assistance. In the United States, some major pesticide companies can provide a clean-up and decontamination team in certain areas; this service has proved to be very helpful.

Spillage incidents should be reported to proper authorities, especially local health officials. There may be situations where officials will find it necessary to take action to prevent movement of a contaminated vehicle or cargo until it is properly investigated or decontaminated. If cargo other than pesticides has been removed from a vehicle in which spillage of pesticides has occurred, the items should be located and checked for contamination. Careful consideration should be given to whether items intended for human or animal consumption should be destroyed, especially if they are in containers that can be permeated by the pesticide. It is necessary to trace the location of cargo that has been reshipped following a spillage incident in order to prevent any hazard to the receiver.

When pesticide spillage occurs, the hazard of the incident should be assessed and precautions immediately taken to prevent additional contamination. The contaminated clothing of an individual that has been exposed to toxic material should be removed as soon as possible and contaminated skin areas thoroughly cleaned with generous amounts of soap and water to reduce dermal absorption. Exposed persons should be placed under medical observation to ensure that any poisoning symptoms will be noted as early as possible so that prompt and proper treatment can be administered. This is especially important where contact has been with one of the more highly toxic organophosphate pesticides.

Waste pesticides, damaged containers and contaminated items should be buried in a location carefully selected to avoid contaminating surface or subsurface water (see chapter 8). If personnel from the pesticide plant are sent to the spillage site as a clean-up crew, they should be instructed to wear proper protective clothing and equipment. Use of cartridge-type respirators and water-repellent clothing, including rubber gloves and boots, are the minimum requirements for the clean-up crew of toxic pesticides. Pesticide contamination through spillage can present a serious clean-up problem. It may be difficult and perhaps almost impossible to decontaminate certain surfaces to the extent that all of the toxic pesticide is removed. For example, if liquid concentrate parathion has been allowed to remain on wood flooring for any appreciable length of time, it is practically impossible to accomplish an adequate decontamination. The solvent used in the formulation apparently helps carry the toxic material into the wood and between the flooring strips to the extent that, in most cases, the only reasonable safety measure would be the removal and replacement of the contaminated wood.

It has been the author's impression from conversations with warehousemen and drivers and from personal experience with spillage incidents that there is a tendency to try to "clean-up" any spillage without contacting the shipper or pesticide company or obtaining other expert advice. The result is inefficient decontamination; lorries or trailers are dispatched on the next assignment, and the spillage area might lose its identity as a potential hazard. Therefore, it is important that personnel involved in transportation and storage of these materials know the proper precautions in handling and shipping toxic chemicals.

When pesticide has been spilled on flooring, the first inclination may be to "hose down" the floor with water to wash away as much of the pesticide as possible. This is not a good practice because flushing with water often spreads contamination over a wider area and causes the seepage of toxic material through the floor. In attempting to remove pesticide from a surface the first step should be to carefully remove as much of the pesticide as possible without enlarging the contaminated area. For dusts or wettable powders, the first step might be as simple as sweeping up the bulk of the material and disposing of it. The broom and other items used in this clean-up operation should be destroyed to prevent future use.

Large quantities of dust or wettable powders should never be picked up with a conventional-type vacuum cleaner with exposed collection bag. The fine inert material may penetrate the collection bag and engulf the operator in a cloud of toxic dust. Commercial vacuum cleaners designed for use in pesticide manufacturing plants are better suited for picking up dry pesticide. They are usually designed so that there is a minimum of leakage into the air during operation. After the first collection of loose material, these vacuum cleaners do a reasonably good job of recovering dry particulate material from seams and cracks in the surface, but it should not be assumed that adequate decontamination has been accomplished without considerable additional cleaning.

The first pick-up of liquid spills should be made by use of an absorbent material such as attaclay, fine sawdust, soda ash or even dry soil. Final decontamination should be with a chemical that is capable of degrading the pesticide. It is in this area of chemical decontamination that added research is needed because some of the materials that have been used for this purpose are not particularly efficient in degrading all pesticides. Some of the more readily available materials that have been used are sodium bicarbonate, household chlorine bleach (sodium hypochlorite), lye (sodium hydroxide) and hydrated lime as well as water and detergent. Furthermore, ethyl alcohol, isopropyl alcohol and trisodium phosphate have been used to clean surfaces.

Decontamination of metal lorry beds is possible if the flooring is continuous without seams or many bolt heads. Most metal lorry floors, however, have seams and are badly gouged and scratched, therefore decontamintaion is very difficult.

A highway accident involving pesticides can present a serious hazard not only to those persons directly involved in the accident but also to those assisting the injured and to workers who clean up the wreckage and highway surface. In such a situation it is well to remember that any persons injured in a wreck should be checked to determine if their skin has become contaminated with pesticide. The removal of highly toxic organophosphate pesticide from the skin may be just as important and urgent as other first-aid measures for an injury. Almost any available liquid may be useful in cleansing contaminated skin in such an emergency. Travellers in waiting automobiles at the wreckage site may have liquids such as water, coffee, soft drinks or a bottle of baby's milk. People travelling in campers or trailers may be able to provide the more suitable pan, soap, water and towel or washcloth needed for a thorough cleaning job. If injured persons have been taken to a hospital without being checked for skin contamination, the hospital should immediately be advised of the possible hazard.

Employees of a pesticide manufacturing plant, who may be called to the scene of such an accident as experts on toxic chemicals, may not only be faced with providing life-saving advice as mentioned above but may encounter other problems associated with such an incident. In order to assess the hazard of the situation it is important to first determine the pesticides involved. If the shipping papers are not available or if they show that several different pesticides are in the shipment, it may be necessary to enter the wrecked vehicle to identify the compounds that are leaking onto the highway surface. At this time the foresight of having protective equipment available for such an emergency will be appreciated. The wearing of waterproof protective clothing and a cartridge-type respirator are the minimum requirements to enter wreckage contaminated with toxic materials. Where highly volatile toxic materials are involved, the use of a self-contained air-supply respirator system is advised. A battery-operated light for checking pesticide container labels in the dark and a shovel for covering spillage with soil are useful items.

The police should not allow unauthorized persons near the contaminated area. Footprints or tyre tracks across an area contaminated with a highly toxic compound should be cause for concern. In such a case, a check should be made to determine if anyone at the site is wearing contaminated shoes. Vehicles with contaminated tyres may be difficult to trace. One method that has been employed in the United States is by radio announcement. Toxic material on a vehicle tyre may present a hazard to mechanics, service-station attendants or small children who may play around parked vehicles.

If the pesticide spilled on the highway surface is a dust or wettable powder formulation, such dry material might be drawn into the ventilation system of a passing vehicle and create a potential hazard to vehicle occupants, especially infants. During windy weather, dry pesticide material can be blown some distance and may cause contamination of nearby areas. Covering dry pesticide with a tarp or moist soil may prevent some movement by the wind; however, strong winds make this procedure ineffective. If a local fire department has equipment at the site, it may be advisable to "wet-down" the material so that it will not be carried by the wind or to flush it from the highway surface. However, this should be done only after careful consideration of the possibility of contaminating nearby streams or bodies of water. If the potential for contamination of such water appears to be greater through movement by wind than by flushing with water, the flushing may be justified. Washing of the roadbed or highway surface, however, spreads contamination and makes final clean-up more difficult. A fire department should not be allowed to flush pesticide down a street storm drain or sewage inlet.

The police may be anxious to learn whether it is safe to allow vehicles to pass a contaminated wreckage site. If there is any doubt about the situation, it would be wise to prevent traffic movement. If there is ample room for vehicles to pass a contaminated area and the compounds involved are relatively non-toxic, there may be some justification for allowing movement of traffic. In this decision, however, a thorough knowledge of pesticide toxicity is important.

Safe removal of the contaminated wreckage and clean-up at the site requires careful management of the activities. If a pesticide company sends lorries and crews to collect undamaged cargo or to dispose of waste pesticides and damaged containers, the workers should wear protective gear and take proper safety precautions. Undamaged cargo should be inspected to determine if it is contaminated. Care must be taken to avoid contaminating additional lorries, or towing equipment that are sent to the scene. As much cleaning of the wreckage as possible should be carried out before it is moved; otherwise there may be further spillage or drainage as the wreck is lifted or towed. A thorough cleaning with absorbent material should be accomplished before any washing with water. Contaminated wreckage should not be moved to any location where it might be a hazard. Thorough additional cleaning should be carried out in a safe location under the supervision of a responsible person. This is especially important if the damaged vehicle will be repaired by mechanics.

In cleaning pesticides from highway or road surfaces, it is advisable to follow somewhat the same procedure as noted above for other surfaces. The procedure should end with a thorough cleaning with water, although run-off into water supplies must be avoided. Contaminated soil, crushed rock or gravel areas should be dug up, and the waste material buried in a safe location.

The site should be visited the following day. By this time the road surface may be dried out, and it is much easier to identify any remaining contaminated areas. After final clean-up, samples should be taken at various locations for analysis as a check for effectiveness of clean-up procedures if a pesticide analytical service is available.

One of the problems related to pesticide storage and transportation is hazard from fire. Fire has been caused by spontaneous combustion of pesticides, and solvents in liquid formulations have contributed highly inflammable fuel to fires. Firemen, police and onlookers at a fire may be subjected to toxic pesticide fumes. During pesticide warehouse fires, there is undoubtedly much incomplete combustion, especially of wettable powder formulations. Thus, the toxic pesticide compound as well as the break-down products may be present in smoke. Up to 7.9 mg of parathion/m^3 of air has been found in the smoke of burning wettable powder parathion from "empty" paper bags containing residues of the pesticide.[10] Although persons near a pesticide fire would not ordinarily be subjected to the fumes for any long period of time, the high concentration from burning bags containing only small amounts of parathion indicates that it may be hazardous to breathe the fumes for even a relatively short time.

Fires in pesticide warehouses and formulation plants have resulted in large quantities of pesticide waste which must be hauled and buried at a safe location. Where stacks of dry pesticide are involved, much of the materials may be only partly burned and, in the centre of tightly packed stacks, some of it may not be even charred. Clean-up crews should be warned of the potential hazard and instructed to wear protective gear when handling such material.

SUMMARY

Wherever pesticides are stored or transported there is a potential hazard because of the possibility of spillage or fire involving material highly toxic to humans. Proper clean-up and disposal of spilled or waste toxic materials require the careful attention of personnel who have a thorough knowledge of such compounds. Personnel from a pesticide manufacturing plant may be called for expert advice and assistance in clean-up procedures. When pesticide spillages or fires do occur, the safety of personnel is of greatest importance. Despite efforts to prevent such hazardous situations, the number of incidents occurring each year indicates that continued vigilance in the field of transportation and storage is necessary in order to prevent pesticide poisonings.

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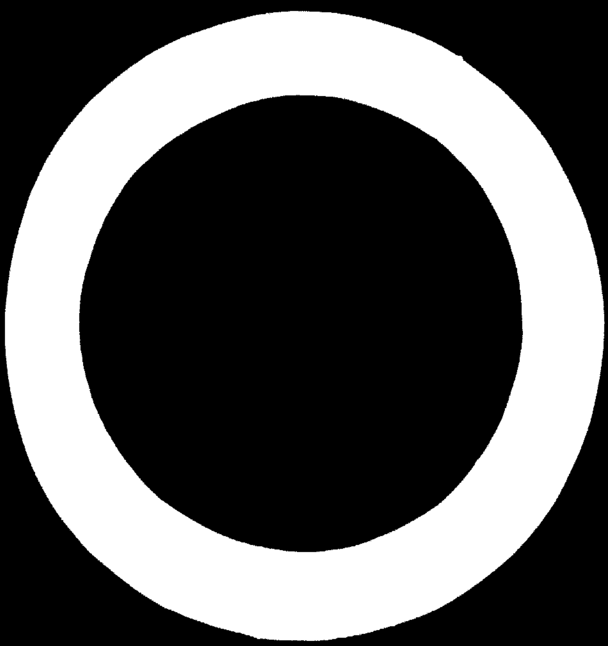
[10] Wolfe, H. R., W. F. Durham, K. C. Walker and J. F. Armstrong (1961) *Archives of Environmental Health*, Vol. 3, p. 531.



10. SAFETY IN THE HANDLING OF ORGANOPHOSPHATE PESTICIDES

*by William V. Andresen**

Organophosphate pesticides have been manufactured and marketed in the United States since 1946, when parathion was introduced. Considerable experience has developed in the handling of these very toxic and potentially hazardous materials with the increasing use of them. Toxicity is the capacity of the material to cause injury or death. Hazard is the probability that injury or death will result from a particular use of the material.

Although the potential hazards to employees engaged in the manufacture of technical grades of pesticides are less than those to persons engaged in the formulation or use of pesticides, the industrial hygiene aspects are the same. Experience proves that the organophosphates can be safely handled if the following basic rules are strictly followed:

Know the materials being handled.

Follow the industrial hygiene precautions recommended by the manufacturers. These include the use of protective equipment and clothing, ventilation for the control of dusts, mists or vapours and proper storage and handling practices. Do not store, carry or consume food, drink or tobacco in the work area.

Follow the personal hygiene practices recommended by the manufacturer. In the case of organophosphates, these include washing thoroughly with soap and water before eating, smoking or going to the toilet and a complete shower and change of clothing at the end of the work day.

Know the signs and symptoms of organophosphate poisoning and acquaint the plant physician and local physician, members of the immediate family and friends with them. If the signs and symptoms occur, call a physician immediately. The physician should, of course, be provided with the recommended method of treatment of organophosphate poisoning.

Undergo periodic blood tests for cholinesterase activity. The absorption of organophosphate in subtoxic quantities can thus be detected and serious illness or death averted.

All of these points are discussed in detail below.

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INDUSTRIAL HYGIENE

Organophosphate pesticides range in toxicity from a slightly toxic product like malathion to highly toxic products like the parathions which are designated as Class I poisons by USDA and Class B poisons by the USDT. Regardless of the degree of toxicity, all organophosphates should be handled carefully, and good industrial hygiene practices should be followed.

Knowledge of product hazards

The first basic rule for the safe handling of pesticides is to know the product being handled. The easiest way to do this is to read the label. Every pesticide container is labelled, and every label contains pertinent safety information. Additional descriptive information can be obtained from the manufacturer. Many companies have published manuals containing recommended manufacturing methods, toxicity data, industrial hygiene precautions, ventilation recommendations and medical information. One company has placed on all of its pesticide packages a STOP sign which warns all users of the material to read the label. For example: on 55-gal drums the sign is on the seal over the drum bung; on all 1- and 5-gal pails of technical materials or formulations it is on the flexspout cap seal. The STOP design shown in figure 1 is similar to the road signs in the United States. Use of this or a similar system by all manufacturers and formulators of pesticides may prove very helpful.

Figure 1. A warning sign for pesticide containers

United States law requires that all pesticide labels contain the following information:

Brand name;
Intended use of the product;
Active ingredients (per cent);

Inert ingredients (per cent);
Directions for use;
Warnings;
Name and address of manufacturer or registrant;
USDA registration number (on formulations). In the case of Class B poison, the USDT requires that a Class B poison designation be a part of the label;
Net content.

A typical organophosphate label is shown in figures 2 to 4. It consists of three panels. The centre portion of the label (figure 2) indicates that the product in the container is technical thimet and shows the ingredients, the USDA poison category, intended use, net contents and advice that the pesticide be kept out of the reach of children. (Unfortunately over the years that pesticides have been used, a large percentage of the deaths due to organophosphates occurred in children playing with or drinking pesticides from original containers, from soda bottles into which excess pesticide had been stored or by contact with incorrectly discarded containers.)

This product label contains the words DANGER and POISON and the skull and cross-bones symbol on the centre portion of the label because it is a Class I poison as designated by the USDA Federal Insecticide Act. Table 1 shows the USDA poison categories.

TABLE 1. UNITED STATES DEPARTMENT OF AGRICULTURE CATEGORIES OF TOXICITY

		Route of admission		
		LD_{50}[a]		*LC_{50}*[b]
Category	*Signal word*	*Oral (mg/kg)*	*Dermal (mg/kg) 24 hr exposure*	*Inhalation (mg/l)*
I "Poisonous if..."	Danger Poison (skull and cross-bones)	0 to 50	0 to 200	0 to 2,000
II "Harmful or fatal if..."	Warning	> 50 to 500	> 200 to 2,000	> 2,000 to 20,000
III "Harmful if..."	Caution	> 500 to 5,000	> 2,000 to 20,000	
IV	None[c]	> 5,000	> 20,000	

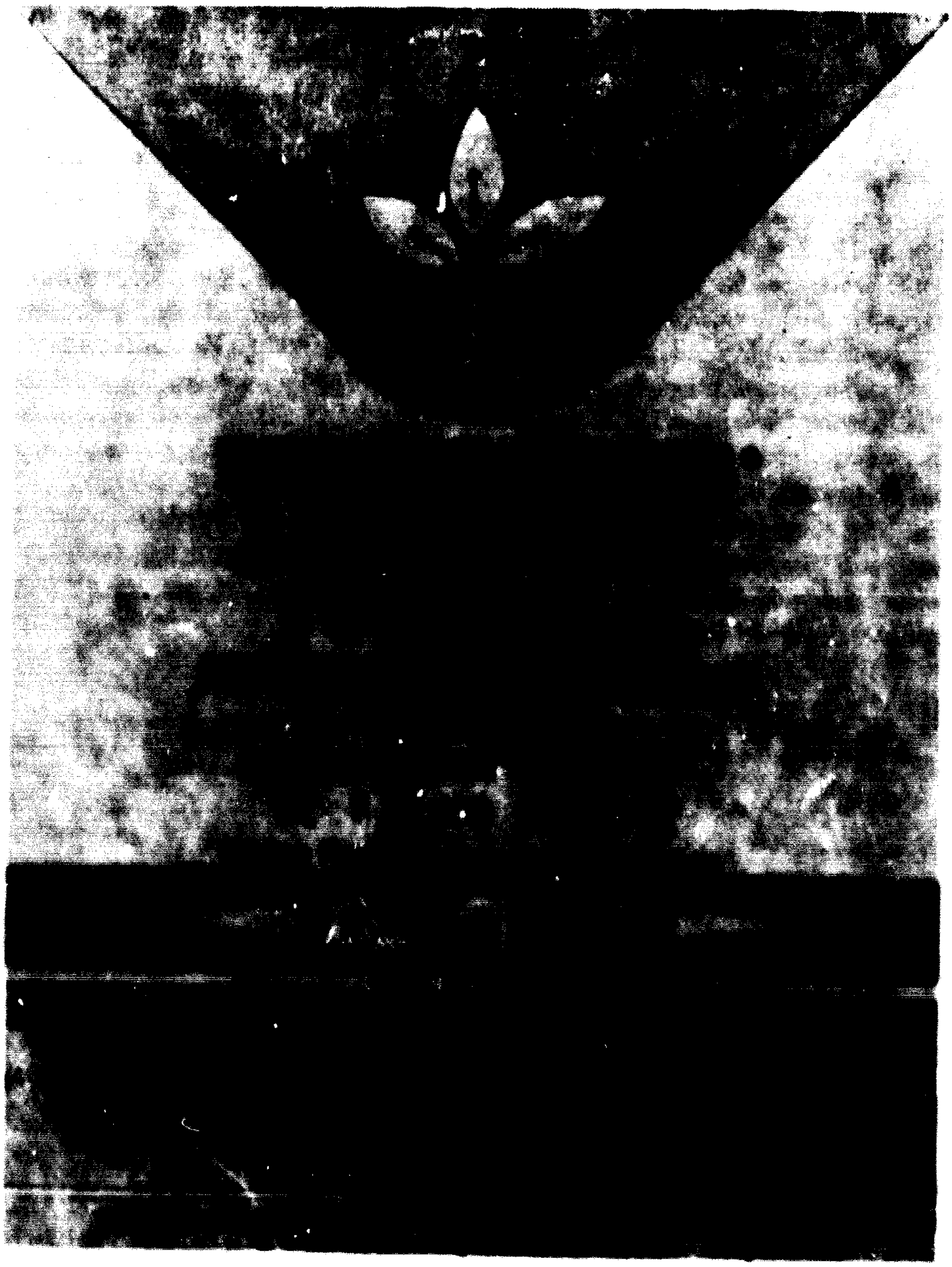
[a] LD_{50} — the dose level which will kill 50 per cent of the test animals. Minimum of 14-days observation. Animals fasted for oral studies.

[b] LC_{50} — the air concentration which will kill 50 per cent of test animals exposed for a period of 1 hour. Minimum of 14-days observation. Vapour or gas may be expressed in ppm.

[c] None required based on acute toxicity; however, the nature of the product and the use pattern may require appropriate precautionary statements.

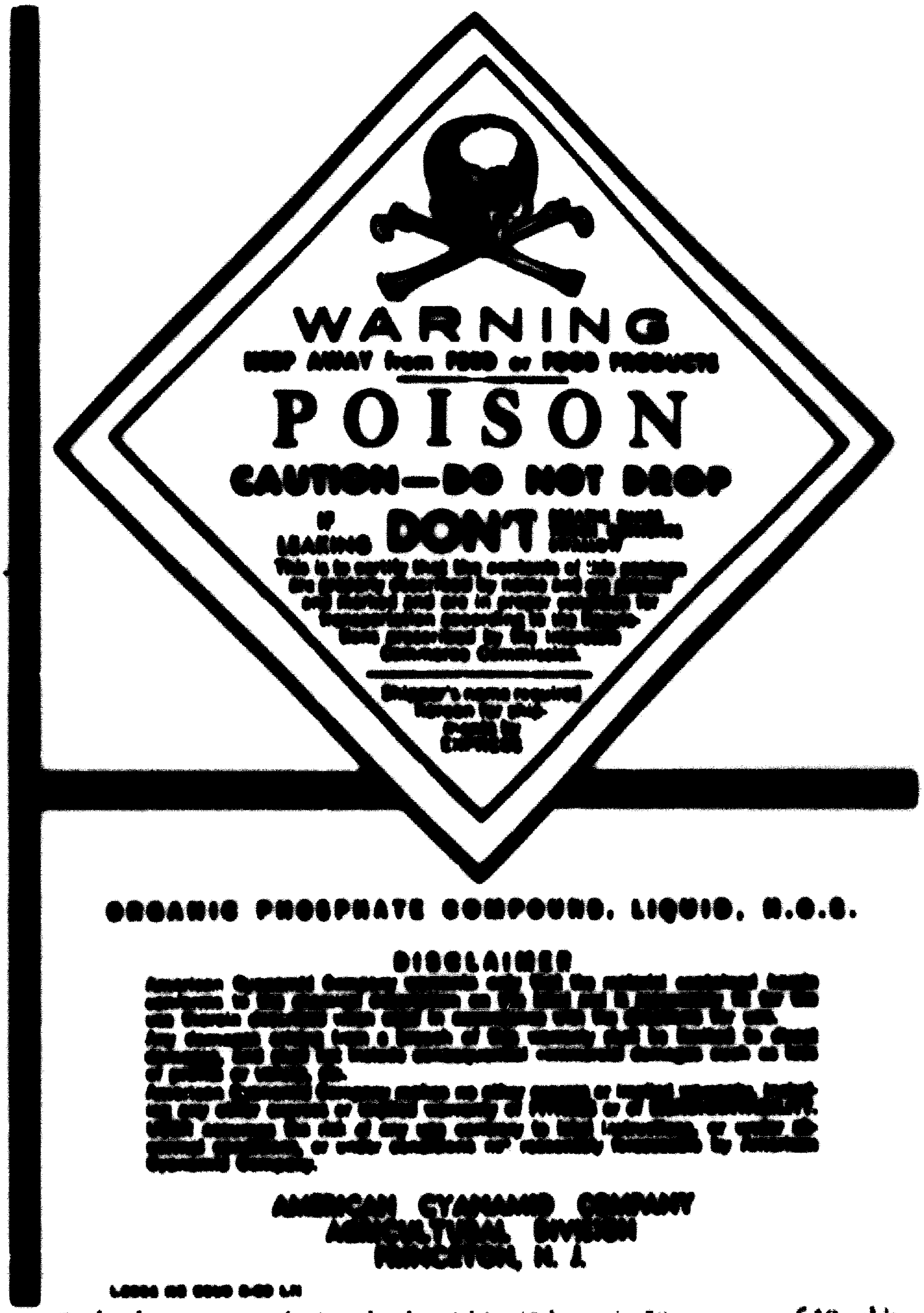
There are four categories of toxicity for the classification of all pesticides. The classification is entirely dependent upon LD_{50} values. The signal words DANGER and POISON, the skull and cross-bones, and the word WARNING or CAUTION are legally required on the label. Anyone who uses technical materials originating in the United States should become familiar with these symbols and the degree of toxicity they denote.

Figure 2. Centre panel of the thimet label



The right panel of the thimet technical label (figure 3) contains the Class B poison warning sign required by the USDT. Class B poisons are liquids and solids which are known to be so toxic to humans as to afford a hazard during transportation. In the absence of adequate data on human toxicity, materials are considered to be Class B poisons and toxic to humans if they fall within any one of the following categories when tested on laboratory animals:

Figure 3. Right-hand panel of the thimet label



WARNING

POISON

CAUTION—DO NOT DROP

DON'T

ORGANIC PHOSPHATE COMPOUND, LIQUID, N.O.S.

DISCLAIMER

AMERICAN CYANAMID COMPANY
AGRICULTURAL DIVISION
PRINCETON, N. J.

Oral substances producing death within 48 hours in 50 per cent of 10 white laboratory rats weighing 200 to 300 g at a single dose of 50 mg/kg of body weight;

Inhalation substances producing death in 50 per cent of 10 or more white laboratory rats weighing 200 to 300 g, when inhaling 2 mg/l or less of vapour, mist or dust for a period of one hour or less;

→

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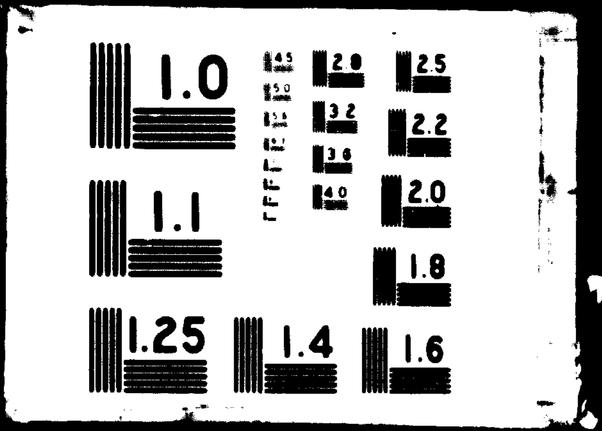
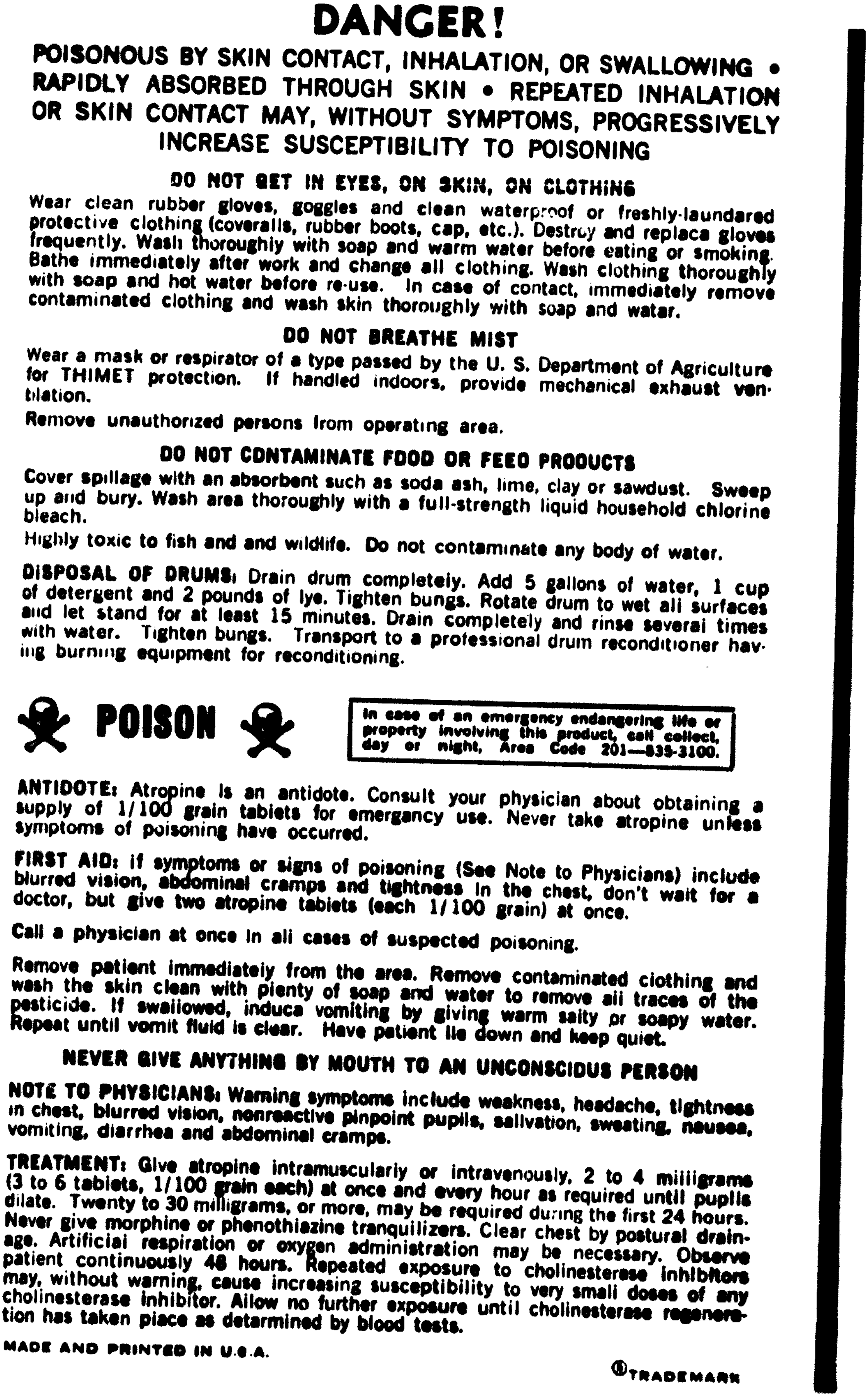


Figure 4. Left-hand panel of the thimet label



DANGER!

POISONOUS BY SKIN CONTACT, INHALATION, OR SWALLOWING • RAPIDLY ABSORBED THROUGH SKIN • REPEATED INHALATION OR SKIN CONTACT MAY, WITHOUT SYMPTOMS, PROGRESSIVELY INCREASE SUSCEPTIBILITY TO POISONING

DO NOT GET IN EYES, ON SKIN, ON CLOTHING

Wear clean rubber gloves, goggles and clean waterproof or freshly-laundered protective clothing (coveralls, rubber boots, cap, etc.). Destroy and replace gloves frequently. Wash thoroughly with soap and warm water before eating or smoking. Bathe immediately after work and change all clothing. Wash clothing thoroughly with soap and hot water before re-use. In case of contact, immediately remove contaminated clothing and wash skin thoroughly with soap and water.

DO NOT BREATHE MIST

Wear a mask or respirator of a type passed by the U. S. Department of Agriculture for THIMET protection. If handled indoors, provide mechanical exhaust ventilation.

Remove unauthorized persons from operating area.

DO NOT CONTAMINATE FOOD OR FEED PRODUCTS

Cover spillage with an absorbent such as soda ash, lime, clay or sawdust. Sweep up and bury. Wash area thoroughly with a full-strength liquid household chlorine bleach.

Highly toxic to fish and and wildlife. Do not contaminate any body of water.

DISPOSAL OF DRUMS: Drain drum completely. Add 5 gallons of water, 1 cup of detergent and 2 pounds of lye. Tighten bungs. Rotate drum to wet all surfaces and let stand for at least 15 minutes. Drain completely and rinse several times with water. Tighten bungs. Transport to a professional drum reconditioner having burning equipment for reconditioning.

POISON

In case of an emergency endangering life or property involving this product, call collect, day or night, Area Code 201—835-3100.

ANTIDOTE: Atropine is an antidote. Consult your physician about obtaining a supply of 1/100 grain tablets for emergency use. Never take atropine unless symptoms of poisoning have occurred.

FIRST AID: If symptoms or signs of poisoning (See Note to Physicians) include blurred vision, abdominal cramps and tightness in the chest, don't wait for a doctor, but give two atropine tablets (each 1/100 grain) at once.

Call a physician at once in all cases of suspected poisoning.

Remove patient immediately from the area. Remove contaminated clothing and wash the skin clean with plenty of soap and water to remove all traces of the pesticide. If swallowed, induce vomiting by giving warm salty or soapy water. Repeat until vomit fluid is clear. Have patient lie down and keep quiet.

NEVER GIVE ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON

NOTE TO PHYSICIANS: Warning symptoms include weakness, headache, tightness in chest, blurred vision, nonreactive pinpoint pupils, salivation, sweating, nausea, vomiting, diarrhea and abdominal cramps.

TREATMENT: Give atropine intramuscularly or intravenously, 2 to 4 milligrams (3 to 6 tablets, 1/100 grain each) at once and every hour as required until pupils dilate. Twenty to 30 milligrams, or more, may be required during the first 24 hours. Never give morphine or phenothiazine tranquilizers. Clear chest by postural drainage. Artificial respiration or oxygen administration may be necessary. Observe patient continuously 48 hours. Repeated exposure to cholinesterase inhibitors may, without warning, cause increasing susceptibility to very small doses of any cholinesterase inhibitor. Allow no further exposure until cholinesterase regeneration has taken place as determined by blood tests.

MADE AND PRINTED IN U.S.A.

®TRADEMARK

Skin absorption substances producing death within 48 hours in 50 per cent of 10 or more rabbits tested at a dosage of 200 mg/kg of body weight on continuous contact with the bare skin for 24 hours or less.

The Class B poison classification for pesticides is essentially the same as the USDA Class I poison. Many materials other than pesticides are Class B poisons.

A toxicity rating chart which equates toxicity to common quantity measurements in United States use is shown in table 2. Table 3 shows a comparison of the LD_{50} values of several organophosphate pesticides in the Class B poison category.

TABLE 2. TOXICITY RATING CHART[a]

Toxicity rating or class	*Probable lethal dose for a 70 kg male (mg/kg)*	
6. Super toxic	Less than 5	(a taste, less than 7 drops)
5. Extremely toxic	5—50	(7 drops to 1 teaspoon)
4. Very toxic	50—500	(1 teaspoon to 1 ounce)
3. Moderately toxic	500—5,000	(1 ounce to 1 pint)
2. Slightly toxic	5,000—15,000	(1 pint to 1 quart)
1. Practically non-toxic	more than 15,000	(more than 1 quart)

[a] The expression of lethal doses in the American system of ounces, pints and quarts is given in parentheses.

TABLE 3. THE LD_{50} VALUES OF SEVERAL PESTICIDES AND A CLASS B POISON

Pesticide	*Oral toxicity (mg/kg)*	*Skin contact toxicity (mg/kg)*
Abate	2030[a]	1930[b]
	2330[c]	970[d]
Dimethoate	185[a]	1000[e]
	245[c]	800[a]
Malathion	2800[a]	6700[c]
		4100[b]
Methyl parathion	14[a]	67[a]
	24[c]	67[c]
Thimet	3.7[a]	6[a]
	1.6[c]	20[c]
Parathion	20[a]	28[a]
		45[c]
		15[b]
Zinophos	12[a]	10[c]
Class B poison	50[a,c]	200[b,d]

[a] Male rats.
[b] Male rabbits.
[c] Female rats.
[d] Female rabbits.
[e] Male guinea pigs.

It can be seen that parathion, thimet and zinophos insecticides are extremely toxic. They are at the lower end of the USDA Class I poison category of toxicity. Small quantities can cause serious illness and possible death. However, the toxicity of a material is not the only factor which should be considered regarding the potential effect of a material on humans or other animals. Manufacturers, formulators and users should consider the hazards in a particular use of a material as well as its toxicity.

As an example, 10 and 15 per cent formulations of thimet 10 G and 15 G on granular clay of 24 to 48 screen mesh size contain an extremely small percentage of respirable size particles in the product. In addition, the material is intended to be drilled into the soil. The hazard has been reduced considerably by this formulation and application. Skin absorption of the granular product is not a serious problem as the granules do not readily adhere to the skin because of their size. In addition, clay tends to bind the technical material by its absorptive capacity. The skin toxicity LD_{50} values for 10 and 15 per cent thimet granules are considerably less than those for the corresponding technical material.

The left panel of the thimet technical label (figure 4) is headed by the word DANGER followed by a long list of precautionary statements which outline the hazards inherent in use of the product and describe how to avoid the hazards. The routes of exposure of thimet are skin contact, inhalation and swallowing (ingestion); skin contact is by far the greatest hazard. With the exception of malathion and abate, toxic quantities of organophosphate compounds are rapidly absorbed through the intact skin.

Many of the newer organophosphates in use have low vapour pressures at ambient temperatures, so that prolonged exposure to even saturated atmospheres is hazardless. The assumption that exposure to a vapour that is detected by the nose presents a hazard is not true. The odour of most organophosphates is detectable even in extremely low concentrations; the mercaptan odour associated with thimet is detectable in parts per billion. Airborne mists, spray or dust particles of the more toxic organophosphate pesticides generated in formulation or applications in the field, however, may present a hazard by inhalation.

Ingestion in occupational exposure is usually "incidental ingestion" which is the repeated introduction of pesticides into the system through contamination of food, drink or tobacco. This may be either directly, by hand contamination or by swallowing dust, liquid, vapour or mist which was previously inhaled and which remained in the upper respiratory passages.

Personal hygiene

The left panel of the label (figure 4) recommends the use of protective clothing to prevent contact of the pesticide with the skin or eyes. It is recommended that clothing be laundered before re-use. Therefore, protective clothing should only be worn one day.

The protective clothing includes underwear, stockings, long-sleeved coveralls or long-sleeved shirt and trousers, and washable cap. In addition to these washable items, the following may be included: rubber gloves, rubber shoes or boots, goggles or face shield and respirator. A number of formulators employ additional safety items such as rubber aprons, air-supply suits and helmets. These practices are excellent but are not always necessary if other aspects of a good industrial hygiene programme are operative.

The daily clothing provision is extremely important and should definitely include stockings and underwear. Clothing contaminated with organophosphates remains contaminated for a long time because of low vapour pressures of the materials and can be a serious source of exposure.

When drums of pesticides are opened in hot weather or in other operations where contact with spray or mist is possible, goggles or a face shield should be used. Leather shoes readily absorb organophosphate pesticides, and, if worn after being contaminated, they provide a significant source of exposure. Rubber gloves should be handled without grasping the portion of the glove contaminated with pesticide. Before removal, gloves should be washed frequently with soap and water and should be decontaminated periodically with household bleach solution. Gloves should be replaced frequently (as often as every 2 to 3 days in a manufacturing plant). It is important to clean and decontaminate rubber footwear, goggles and respirators frequently. This can be accomplished by washing with liquid bleach followed by soap and water.

The left panel of the label (figure 4) recommends thorough washing with soap and water before eating or smoking and bathing after a work day and then a complete change of clothing. Personal hygiene is extremely important; one of the most important parts of the industrial hygiene programme is personal washing. The shower at the end of the work day must be a mandatory work condition. If a worker refuses to take a shower, he should not be permitted to work with the extremely toxic organophosphates. The shower should be thorough and include the hair on the head. The label warns that in case of skin contact due to contaminated clothing during the work day, the clothing should be removed immediately and the skin washed thoroughly with soap and water. A thorough shower and a change of clothing are advisable.

The next warning on the left panel is DO NOT BREATHE MIST. Wear a mask or respirator approved by the USDA for thimet protection. (The responsibility for the approval of respirators has been transferred from the USDA to the United States Bureau of Mines.) Respiratory protection should be used where there is a chance of exposure to dust in formulations. The label recommends the use of mechanical exhaust ventilation if thimet insecticide is used indoors, which means in solid or liquid formulation operations during dumping, blending, transferring and packaging.

The best way to prevent incidental ingestion is to prohibit the carrying of drink, tobacco or food on the person when working with organophosphates and to prohibit storage or eating of food in areas where the pesticide is stored or used. Washing with soap and water before eating is essential. The food-handling area should always be separated by at least a doored wall with the door kept closed when not being entered. Where dust containing organophosphate insecticide is generated, a lunchroom adjacent to the work area should be kept under positive pressure to prevent dust from entering it.

The next item on the label reads DO NOT CONTAMINATE FOOD OR FEED PRODUCTS which means in essence do not store pesticides near products intended for human or animal consumption. Disposal methods for spillage of material and for empty drums given on the label have been described in chapter 9.

Medical aspects

The rest of the left panel of the label (figure 4) describes the symptoms and signs of organophosphate poisoning, first-aid procedures and treatment of poisoning. The symptoms and signs of organophosphate poisoning include the following: headache, blurred vision, constricted pupils, weakness, nausea, abdominal cramps, diarrhoea, feeling of tightness in chest, excessive sweating and excessive salivation.

These signs and symptoms should be learned by all employees and their families. If the symptoms occur, a physician should be called immediately and informed that the affected person works with organophosphates; the antidote is atropine or 2-PAM. All people handling pesticides should provide doctors servicing their operations with medical information on organophosphate poisoning and treatment which is contained in many publications which are readily available.

If symptoms occur on the job, the affected person should be removed from the work area, stripped of contaminated clothing and the skin washed with an abundance of soap and water to remove all traces of pesticide. If the pesticide has been swallowed, vomiting should be induced by giving warm, salty or soapy water, and the treatment repeated until vomit fluid is clear. Vomiting may be induced by sticking a finger down the patient's throat. The patient should be made to lie down and drink large quantities of water, while being kept warm and quiet; however, *nothing should ever be given by mouth to an unconscious person.*

The antidotes for organophosphate poisoning are atropine and 2-PAM. The latter is administered intravenously by a physician. Many companies handling these pesticides have a supply of 1/100-grain atropine tablets available for emergency use. If symptoms occur, two atropine tables should be given orally at once. *If atropine is given, a physician must be called;* the employee should not be treated without professional assistance being sought.

The remainder of the label contains the note to a physician describing the signs and symptoms and treatment which is to be administered by him. The three major facets of treatment are:

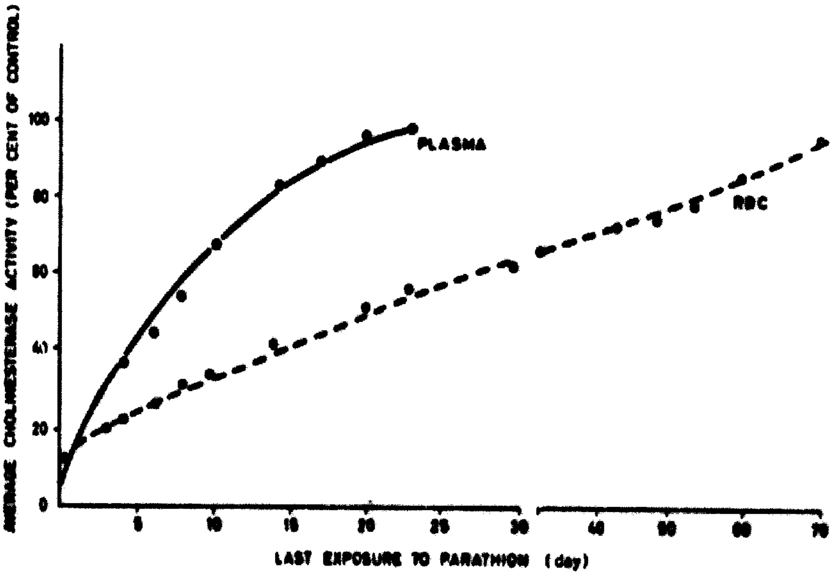
Maintenance of respiration (mouth-to-mouth respiration);
Termination of exposure (clothing removal, washing and removal of the individual from the area);
Administration of antidote (complete atropinization).

The label indicates that repeated exposure to cholinesterase inhibitors may cause increased susceptibility to very small doses of any cholinesterase inhibitor without warning. Therefore it is desirable to monitor the exposure of persons working with organophosphates for relatively long periods of time by a blood testing programme which is discussed below.

Red blood cell cholinesterase regeneration is relatively slow as shown in figure 5 for parathion. Serum cholinesterase regeneration is relatively rapid. Anyone with low cholinesterase activity, regardless of whether signs and symptoms are evident or not, should be removed from further exposure to organophosphates until cholinesterase regeneration has taken place as determined by blood tests.

All employees should have periodic blood tests. The Michel electrometric

Figure 5. Rates of regeneration of cholinesterase activity in plasma and red blood cells following inactivation by parathion



method can be used for pre-exposure levels and the Becton Dickinson unopette[1] cholinesterase tests for periodic screening. The latter test is inexpensive, rapid and excellent, but it should be used for screening purposes only as it measures whole-blood cholinesterase. If a low value is found in screening, the blood should be checked again by the Michel method. Confirmation of the low value indicates that the operator should be removed from organophosphate exposure until his level returns to normal as indicated by subsequent tests.

SAFETY IN TRANSPORTATION

Leakage

One of the pressing problems in the pesticide industry at present is the leakage of packages in transit[2] from the manufacturer to formulator or warehouse, or from the formulator to a warehouse or the user. Leakages can occur from a number of causes. One is faulty fabrication of the container, such as poor welding of the side seam or improper gluing of the walls of paper bags. Leakage from this cause may be reduced since the manufacturers of containers have reportedly improved their fabrication and testing techniques.

A second cause of pesticide leakage in transit is poor handling in loading or unloading of the containers from the trucks or railway wagons. There have been a number of incidents in which 55-gal drums or bags of pesticide have been

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[1] Unopette is the registered trade mark of Becton Dickinson Company, Rutherford, New Jersey.

[2] See chapter 9.

pierced by the fork of a fork-lift truck. Other examples of poor handling include dropping of metal containers or cardboard cartons, especially those containing glass bottles. It is important to stress to all personnel the necessity to handle the packages with utmost care.

A third cause of leakage has been the use of an incorrect container for a pesticide or pesticide formulation. There have been a number of incidents of leakage of pesticide containers in the past due to corrosion of the container causing pin-hole leaks in the head of the containers. Substitution of containers with a different type of lining has mainly solved this problem.

Improper loading of pesticides has been a source of damage to pesticide containers with subsequent leakage. There have been numerous incidents where shipments have been improperly braced with resulting container shifting and container-to-container contact. The loading of 55-gal drums on top of one another usually results in leakage in the drums on top from bouncing during transit. Only floor loading is recommended for 55-gal containers.

Although all of the containers used for pesticides must conform with United States Interstate Commerce Commission (ICC) regulations and in many cases are superior to ICC specifications, pesticide companies are working with the container manufacturers for improved packaging to minimize breakage and subsequent leakage. The National Agricultural Chemicals Association (NACA) is a trade association of which most major pesticide manufacturers are members. It has a special committee presently working on container design to minimize breakage.

Transportation procedures

It is best to transport a full shipment of 30- and 55-gal drums of technical material in hydrocushion railway wagons to minimize shifting and drum-to-drum contact. Rather than a full load, only a prescribed number of drums per wagon should be permitted to ensure proper loading and dunnage. Prior to shipment, the closure of each drum should be checked and a cap seal installed over the bung closure. In one instance, a railway wagon of technical thimet was involved in a derailment. Inspection of the wagon showed no damage to the contents probably due to the above method of loading. It was placed upon a new undercarriage and sent to its destination. No leakage was noted at the destination.

Photographs should be taken of all loads after the completion of loading, prior to shipment and at the destination if damage has occurred during shipment. One function accomplished by this photography is to ensure that warehouses and formulators pack the material properly for shipment. If anything happens during shipment, and it occasionally does, the photographs can be compared and events reconstructed.

Lorries are used only if hydrocushion railway wagons are not available. The lorries are loaded with a full floor load to minimize the amount of other materials shipped together with the pesticide freight. However, the manufacturer has no control over what freight is shipped with organophosphate pesticides by a common carrier since even a full floor load does not represent a full legal weight load. The practice of shipping drummed pesticides on flat-bed vans has a high potential for hazard. It has been recently recommended that ICC regulations be amended to prohibit this practice.

Formulations in 30- and 55-gal containers are transported in the same manner as technical material; 5- and 1-gal (four to a carton) pails are usually shipped in trailers. Again, it is desirable to photograph the loaded trailer prior to shipment and at the destination to determine if anything has happened to the shipment during transit. Results from use of piggyback trailers in shipment of 5-gal pails thus far have been excellent.

Companies have been concerned with potential hazards in the event of a transportation disaster such as railway and trailer wrecks or fires in which organophosphates as well as other pesticides are involved. One company uses the following emergency procedure.

All bills of lading have an emergency telephone number to be called in case of accident or fire involving their materials. All trucking and railway companies have been advised of the emergency procedure and its purpose. The telephone is only for emergencies and is manned 24 hours a day. The person answering the telephone has a list of pertinent questions which he asks the caller. All company products are listed by division and the receiver of the call at the headquarters relays the information to the divisional representative. Each division is prepared to handle emergencies involving its products and the call to the emergency telephone activates the procedure. Depending on the extent of the emergency, various company experts may become involved either by telephone or by their presence at the site to aid in decontamination of spills, disposal of wrecked or burned products, salvage operations and advice to fire departments and hospitals. The emergency procedure provides that at least one company representative be present at the scene of the emergency as soon as possible.

The trade association NACA and company members are investigating the feasibility of a nationwide pesticide safety team network to handle emergencies involving Class B pesticides. Thus companies will aid each other, as well as assist police, health and fire departments in emergencies.

Warehousing

The warehousing of organophosphates may be hazardous as evidenced by an incident in Tijuana involving parathion (see chapter 9). Products are stored in warehouses belonging to the company, distributors and the public that are adjacent to areas of use. Warehousing is made as safe as possible by providing literature describing recommended warehousing practices, safety precautions, decontamination and clean-up procedures, advice to firemen and medical information for local physicians or clinics. A basic list of warehouse safety rules follows:

Inspect containers for leaks before handling them;
Do not mishandle containers and thereby create emergencies by carelessness;
If a leak or spill does occur, keep bystanders away and report it immediately;
Do not store organophosphates next to food or other articles intended for consumption by humans or animals;

After organophosphate pesticides have been unloaded, inspect vehicle for contamination; do not release a contaminated vehicle;
Do not release other freight which has been contaminated with pesticides;
Consult shipper or manufacturer for decontamination procedures;
Where Class B poisons are involved, notify USDT.

A manual published by NACA[3] applies in general to all organophosphates. It is highly recommended to all persons concerned with the storage of pesticides.

Ideally, a warehouse for pesticides is fireproof, equipped with a sprinkler system, well ventilated and located in an area remote from residential areas and watercourses. Companies attempt to find this kind of storage, but a warehouse which satisfies all these conditions is often difficult to locate. In warehousing, ideally, pesticides should be stored in a separate room from other products intended for human or animal consumption and separated from other products by an aisle at least 8 to 10 feet (2.4 to 3 m) wide. In a further effort to prevent contamination of other material, specially painted pallets for pesticides are to be used only for those compounds.

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[3] National Agricultural Chemicals Association (1968) *Safety in the Warehousing of Parathion*, Washington, D.C.

11. THE ROLE OF THE FOOD AND DRUG ADMINISTRATION IN REGULATION OF PESTICIDES IN THE UNITED STATES*

The United States is committed by law, policy and the traditions of many decades to assure that the food supply of the nation is safe, clean and wholesome. The United States is committed to full enforcement of these laws, and, accordingly, has developed criteria and protocols that are effective, workable and enforceable. Within this primary goal, the United States seeks means that will permit achievement with minimal dislocation of production or trade. But under no circumstances will hazard to humans or to the environment be countenanced to serve economic goals.

The wholesomeness of any food supply depends in part on the quality of the total environment—the soil, water and air in which the food is grown, processed and consumed. Acute contamination of these basic natural resources by pesticide residues and other pollutants can affect not only the safety of food products but also other environmental values such as human water supplies, wild-life preservation and outdoor recreation. The United States is actively seeking to protect and manage these resources in the interest of greater safety and human welfare.

In the highly interrelated, interdependent world of modern technology and trade, the challenge of protecting crops and livestock from insects, diseases, weeds and other pests without hazard to humans, animals or their environment requires the combined and sustained efforts of scientists, technicians and administrators; of producers, processors and distributors; of industry and government; and of countries working together to establish and administer sound, acceptable standards of food safety and environmental quality.

The statutory authority for the regulation of pesticides and pesticide residues entering interstate commerce has been established by the Congress of the United States. Under these statutes, the responsibility for registration of pesticides and pest control materials has been delegated to the United States Department of Agriculture (USDA). The establishment of tolerances for pesticides in or on human food and animal feeds has been delegated to the Food and Drug Administration (FDA), Department of Health, Education, and Welfare. The following information provides a statement of the authorities on which the American pesticide regulations are based, the criteria for registration and establishment of tolerances, the research, action and education programmes related to pesticides and the existing levels of pesticide residues in the United States.

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* Based on material furnished by the United States Food and Drug Administration.

Food, Drug, and Cosmetic Act

The establishment of tolerances for pesticides on or in food and feedstuffs is provided for in the Pesticide Chemicals Amendment and Food Additives Amendment of the Food, Drug, and Cosmetic Act (Sections 408 and 409) administered by the FDA. The paramount purpose of this act is to assure the safety of the national food supply; to require that the industry promoting the use of the pesticide chemical prove that the residues remaining on the food are safe for the consumer and to require federal clearance before the pesticide is used. The act provides for seizure and destruction of agricultural commodities that contain pesticide residues in excess of established tolerances. Where no tolerance has been established, commodities carrying residues in excess of established working levels are subject to seizure and destruction. The act provides for criminal penalties for violations and the use of a legal injunction.

The act outlines in general terms the data and information to be furnished and procedure to be followed for obtaining a pesticide tolerance. Additional procedures and more specific data requirements in the regulations ensure that food-safety requirements are met prior to establishing a tolerance.

The role of the FDA

If the product is proposed for use in a manner which is likely to result in residues in or on food or feed, it is not registered by the USDA until a tolerance or exemption has been granted by the FDA. The determination of the safety of a tolerance is a scientific judgement and cannot be derived from any arbitrary mathematical calculation. This judgement involves consideration of the "no-effect" levels demonstrated in the experimental animals, the cumulative potential, the metabolic data and the maximum contribution to the diet that could be expected if all commodities for which tolerances are sought bore residues at the tolerance levels. This takes into account any reduction in residues accomplished in preparing the food for consumption, the probable exposure to other similar toxicants and species differences in interpreting the animal data for possible effects on humans. An adequate margin between the tolerance level and the no-effect level in the experimental data is required taking into consideration the proportion of the diet involving crops on which residues might be expected.

Tolerances established under section 408 of the Food, Drug, and Cosmetic Act are established on raw agricultural commodites and not on processed foods. If the residues remaining in a processed food have been removed to the extent possible in good manufacturing practices and do not exceed the tolerance on the raw product, the processed product complies with the law. In general, the residues in processed foods are a fraction of the amount permitted on the raw agricultural commodity. To cover the residues of pesticides applied to or concentrated in processed foods, tolerances may be established under section 409 of the act (the Food Additives Amendment). However, the major uses of pesticides in the United States are on raw agricultural commodities, and the overwhelming majority of established tolerances are on these products.

Ideally, the tolerances on pesticide residues should apply to the ready-to-eat food on the dinner plate because it is the quantity of pesticide actually consumed that can have health significance. However, tolerances established at this point in the food chain would not be practical. Therefore, a point in the distribution system has been selected where meaningful corrective action can be taken to prevent consumption of unsafe amounts of pesticide chemicals. The tolerance concept does not anticipate as a practical matter that all foods will contain residues of all chemicals as high as the established tolerance level, or even that the entire harvest of a single food will always contain a residue at the tolerance level.

Data requirements for pesticide tolerances

The criteria and data requirements for establishing tolerances are described in detail, although some flexibility is permitted in practice. The basic requirement is that the furnished data, when evaluated as a whole, will establish the safety of the proposed pesticide tolerance. This judgement is made by toxicologists qualified by training and experience to evaluate the safety of pesticide residues in food.

Chemical data

The chemical data in pesticide petitions must meet the following major requirements:

> The residue data must delineate the identity and magnitude of the residues and must show that, under the proposed conditions of use, the proposed tolerance is suitable (i.e. will not be exceeded and is not higher than necessary). The analytical methods used to obtain the residue data must be valid and must afford a measure of the total toxic residue. A suitable method must be furnished for enforcing the proposed tolerance.

The following data are usually necessary to arrive at a scientific judgement as to whether these requirements have been met:

Pesticide chemical. The identity and complete composition, including minor components and impurities, as well as accepted chemical (or biological) and common names are required. Specifications must be furnished if required to establish identity or to limit impurities. Chemical, physical and biological properties pertinent to the evaluation of the efficiency of analytical procedures and the nature and stability of residues must be reported.

Conditions of use. Complete proposed directions for use must be included. Proposed limitations and restrictions, such as against feed use of by-products, must be reasonable, practicable and in conformity with accepted practices.

Analytical methods. The petitioner must present or refer to a method suitable for enforcing the proposed tolerance. This method is added to the FDA *Pesticide Analytical Manual*, which is a compendium of pesticide analytical methods. In some instances residue data may be obtained by methods not suitable for regulatory purposes. It is desirable to confirm residue results by using more than one method (i.e. by a specific method and one or two appropriate general methods).

Descriptions of methods must be sufficiently detailed and well organized to be followed by analysts not familiar with the procedures.

General requirements for methods. Extraction and clean-up procedures must be efficient in removing and recovering residues from samples. Methods must be validated by an adequate number of blanks (untreated crops) and recoveries on an adequate representation of the commodities involved. Blank values must be reasonably low in relation to the proposed tolerance. Recoveries must be at appropriate fortification levels in relation to the proposed tolerance and must be reasonably quantitative. Sensitivity, accuracy and precision must be satisfactory in relation to the proposed tolerance and to the toxicity of the pesticide chemical.

Additional requirements for regulatory methods. The methods must meet the following additional requirements: be sufficiently specific to identify and measure residues in the presence of other pesticides which could reasonably be expected to be present on the same commodities; be reasonably rapid and not require "exotic" (unavailable) equipment or reagents; do not require use of untreated crop samples for blanks or internal standards; give satisfactory results when employed by regulatory laboratories. Method trials in at least two FDA laboratories are made to determine the suitability for regulatory purposes.

Samples for analysis. The samples must reflect the proposed conditions of use including maximum use with respect to dose, timing and number of applications. Samples reflecting exaggerated conditions of use are valuable. The conditions under which samples were treated in the field and the method of application must be reported. The samples must reflect adequate geographical distribution (i.e. major growing areas) and an adequate representation of types of crops for which tolerances are proposed.

The time between sampling and analysis and the conditions under which the samples were stored must be stated. The storage time should be as short as possible; if crop or extract samples were stored before analysis (i.e. trimmed, washed, brushed, peeled or hulled) this must be reported. If these operations are necessary to reduce residues within the proposed tolerance, they must reflect commercial practice in preparation of the crop for shipment in interstate commerce.

Analytical results. In all cases individual results and not just averages must be reported. Any corrections for blanks and recoveries must be explained. There must be an adequate number of results for each commodity. The identity and magnitude of the residue under the proposed conditions of use must be established. Toxic residual metabolic, degradation or other conversion products must be identified and measured.

Data showing whether the pesticide is systemic (i.e. translocated within the plant or animal) must be presented. Data must be included to show the rate at which the residue dissipates on the crops involved. Results must include pertinent data on the distribution of the residue (for example, between peel and pulp) and evidence as to whether the residue is reduced when the raw commodity is prepared for market (by washing, trimming or brushing) in order to judge the amount of residue that is likely to remain on the edible portion of the commodity. Where pertinent to the proposed use, data must be presented on the accumulation, persistence and identity of residues in soils, and the transfer of such residues to crops likely to be grown in the same soils. Where pertinent, evidence must be presented to show whether residues concentrate at a higher level or undergo chemical change in processed foods or feeds, including edible by-products.

In certain cases, it may be necessary to provide data showing the effect on residues of standard operations of food preparation for consumption (i.e. cooking). For feed and forage items including feed by-products, there must be a basis for determining whether residues will transfer to food products such as meat, milk and eggs. If so, the identity and magnitude of such transferred residues must be established and suitable tolerances proposed.

Negligible residue tolerance. The guidelines for the review of the chemical data in petitions which propose negligible residue tolerances are generally the same as those described above, except that: *(a)* tissue residue studies on laboratory animals may be accepted to show the likelihood that the pesticide use will result in residues in meat and milk; and, *(b)* tolerances may be established on the basis of a group of crops rather than on each crop individually. A negligible residue tolerance is a tolerance that has been established to provide a basis for registered uses which previously have been accepted on the basis that no residue or a zero residue will be present in the treated crop at the time of harvest. Based on a recommendation from a committee of the National Academy of Sciences-National Research Council, FDA and USDA have abandoned the concept of no-residue or zero-tolerance registration of pesticides as far as possible (for example, only zero tolerances can be established for carcinogens) and have replaced no-residue and zero tolerances with small finite tolerances (i.e. negligible residue tolerances).

Regulatory problems arose because extremely sensitive analytical methods had been developed which indicated that many of these older, no-residue uses did indeed result in low-level residues (see chapter 4). Where a registration had been granted on a no-residue or zero-tolerance basis, one-year extensions of registration had been granted under certain conditions. These extensions were granted when the registered use pattern indicated that there would remain only low-level residues, which are generally recognized to be without toxicological significance. During the one-year extension, the petitioner is expected to document the level and toxicological safety of the residue for the establishment of the negligible residue tolerance. In specified instances, a temporary tolerance is established to permit experimental pesticide field trials on a limited scale conducted in accordance with and required by a temporary permit issued by USDA. The purpose of these trials is to determine the usefulness of the pesticide without destroying the crop.

Toxicological data

It has been determined that a negligible residue tolerance is sufficiently limited by the magnitude of the residue, extent of use and mode of use so that the levels of ingestion which result are considered to be of little or no toxicological significance. The safety factor is usually about 2,000 based on 90-day studies; it is derived as follows:

$$\frac{\text{Quantity of pesticide that produces no effect in the most sensitive animal tested}}{\text{Quantity of pesticide expected in the human diet}} = 2{,}000.$$

Quite often, such tolerances reflect the sensitivity of the method. For such a negligible residue tolerance, the basic requirement is data from two 90-day (subacute) animal feeding studies. The term "basic requirement" is used because acute data for significant metabolites may indicate the need for further studies, the results of the basic 90-day studies may require further work, or knowledge of the toxicity of the general class of compounds involved may result in requests for specific toxicological data.

A tolerance for residues in excess of negligible residues will require the following data. To establish a tolerance for residues in excess of negligible residues, experiments are necessary on at least two animal species with three dosage levels and a control group. The groups at the start of the experiment should be sufficiently large to assure an adequate number of survivors at termination. For rodents this may vary from strain to strain; therefore the number to be used is contingent on the judgement of the investigator. There should be observations of growth, food consumption, general appearance and behaviour, mortality and organ weights. Clinical-laboratory tests (blood and urine, organ function, enzymatic and metabolic) should be performed as well as gross and microscopic examinations. All animals dying before termination of the experiment should be recorded and examined microscopically.

The following data are necessary to establish tolerances for residues:

Acute toxicity. The LD_{50} values should be determined and the signs of toxicity should be described.

Short-term toxicity (subacute toxicity). The duration of these tests is 90 days. One of the three dosage levels should be toxic. Cholinesterase inhibition and demyelination studies are required for organophosphate and carbamate pesticides.

Long-term toxicity (chronic toxicity). One non-rodent species should be used. The duration is usually two years. One of the three dosage levels should be toxic.

Biochemical data. There should be observations of absorption, distribution, metabolic transformation, elimination and possible accumulation. The effect of enzymes should be examined because of the nature of the chemical under study. Metabolic data of pesticides and their other conversion products in treated plants should be recorded. At least acute and short-term toxicity data on the significant plant metabolites or other conversion products are necessary. If the conversion products are different from metabolites of the test animals, long-term toxicity data on the pesticide metabolites or other conversion products may be required.

Reproduction studies. Preferably two animal species should be used and at least two dosage levels and a control group. One dosage level should be definitely toxic; the other level should have no effect. Usually three successive rat generations are observed; two generations are satisfactory if the results are conclusive. There should preferably be two litters per generation. Both males and females should be treated for 60 days prior to breeding. The second and third generations are treated from weaning throughout the breeding period. The necessary data are fertility, length of gestation, live births, still births, survival at four days and at weaning, sex of newborn and of weanlings, body weights, gross abnormalities, and microscopic and skeletal examinations of young in the last generation.

Human data. They include data on industrial exposure, accidental poisonings and suicides, and in special cases the data from controlled experiments. Biochemical data of the type indicated above are particularly useful.

Additional studies. The results of any of the above studies might indicate the need for specific additional studies.

Policy on tolerances

Data requirements for tolerances are subject to continual review in light of new scientific data and information; advances in scientific knowledge of the criteria for the evaluation of the safety of chemicals in food are especially helpful. The data requirements outlined above are the present requirements. Earlier tolerances were established on the basis of fewer data, but any deficiencies are being remedied before tolerances on additional crops are established. For example, the requirement for reproduction studies was instituted in 1963.

There may be some misconception about the method used to determine a tolerance on a raw agricultural commodity. First, it is of essential importance that the tolerance must be safe for the consumer if all of a particular raw food did bear residues at the tolerance level. The FDA takes into account the patterns and modes of consumption, e.g. the proportion of food consumed in the raw state as compared with the proportion consumed in the state where a reduction of residues may occur. It should be emphasized that there must be an adequate margin of safety between the no-effect level in the most sensitive test animal and the level of residue likely to be ingested by the consumer.

Secondly, the tolerance does not reflect the average residue on the raw agricultural commodity; it reflects the maximum residue which will remain on the treated crop as harvested and shipped when the directions for use are followed, if such maximum residue is safe. Pesticide surveillance and enforcement data clearly show that only a small percentage of food samples contain quantities of pesticide residues that actually approach the tolerance levels. This is to be expected, since not all crops need treatment. Tolerances are established to cover the residues (if they are safe for the consumer) that will be present after the maximum number of applications to the crop. The last application is not later in terms of "days prior to harvest" than the label permits. Not all crops in a specified geographic area and certainly not all crops in other growing areas of the country would be attacked by insects at the same stages of growth; even if this situation did occur, growers would undoubtedly choose different, effective pesticides. The United States tolerances have been established primarily to protect the consumer. Sample analyses show that this purpose is being achieved, and at the same time, the grower is permitted to use chemical tools effectively to produce a wholesome and abundant food supply.

Thirdly, since the tolerance is established on the raw agricultural commodity, it does not realistically reflect the residue on the food as eaten except in special cases. Data clearly demonstrate that pesticide residues are substantially reduced by the various processing operations employed in preparing food for consumption (ready-to-eat) e.g. the milling of grain, a washing operation, the peeling of fruits and vegetables, the removal and discard of outer leaves of leafy vegetables, cooking or canning.

Finally, the tolerance will not be set higher than the level reasonably required to cover the residue likely to result from the proposed pesticide use even though the animal-feeding studies may indicate that a higher level is safe. For example, if 10 ppm of a pesticide would be safe as gauged by all the animal studies, but the maximum residue incurred by the proposed use will not exceed 1 ppm on the raw agricultural commodity, the tolerance will be established at 1 ppm. The purpose of FDA is to minimize consumer exposure to pesticide residues in the food supply.

The granting of a registration

If USDA requirements are met and FDA establishes the tolerance, registration is granted. If the safety data do not justify the proposed tolerance, a lower tolerance or a zero tolerance may be established. The USDA then grants a registration on the basis of the tolerance established by FDA provided the pesticide is useful under the conditions required by the lower tolerance.

When a pesticide was registered for use on a food or feed crop on the basis of a zero tolerance or a no-residue basis, the directed use would not leave residues on the harvested food at levels which could be detected by chemical analysis. This has often meant that the development of a more sensitive method invalidated the zero tolerance or no-residue acceptance. The procedure has been modified in favour of registration on the basis of finite tolerances for all uses involving food or feed where there is a reasonable expectation of some residue, however small, as provided for in the joint statement of 13 April 1966 by USDA and the Department of Health, Education and Welfare. Uses involving no reasonable expectation of residues in the food are usually designated "nonfood" uses.

Sampling and enforcement activities

The FDA has several programmes concerned with pesticide residues. The basic purpose of all of them is to ensure the safety of the national food supply. The programmes include a total diet study, as well as research, surveillance and enforcement programmes.

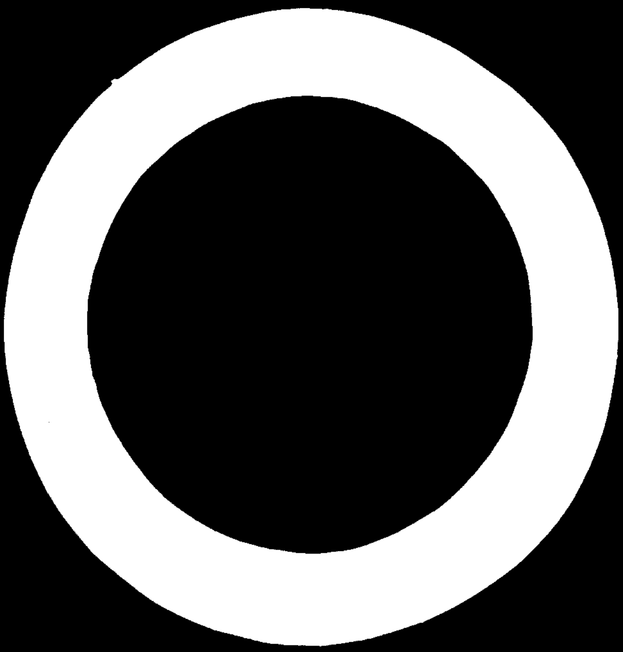
The FDA obtains market basket (or total diet) samples of foods from retail stores bi-monthly in five regions of the country. The samples are prepared for consumption and examined for pesticide residues at sensitivity levels substantially lower than those used in the examination of surveillance and enforcement samples. Much additional analytical time is required to obtain these lower levels of sensitivity and to confirm the results. The proportion of individual food items used in this study was developed by the Household Economic Research Division, USDA, based on the high consumption level of a 16- to 19-year-old male. The quantity of this diet is approximately double that of an average individual. The results obtained from this study are encouraging. In no case does the daily intake of any pesticide chemical exceed the acceptable daily intake recommendation of FAO and WHO. For practically all pesticide chemicals the daily intake is substantially lower than these recommendations.

The FDA surveillance and enforcement programmes were expanded substantially beginning in 1963. For several years, the FDA examined approximately 25,000 samples, in addition to inspection of the food-growing areas to determine the actual practices being followed. Limited resources coupled with relatively low incidences of violations in most food categories have resulted in a reduction in the sampling and inspection programme. Quantitative multi-residue methods of analysis capable of detecting residues at a level of 0.03 ppm were in general use beginning in 1964. These multi-residue methods can detect and measure more than 60 of the common organochloride and organophosphate pesticide chemicals that may occur in samples. A majority of the samples collected and examined under these programmes were classified as objective, which means they were collected without suspicion of excessive residues or misuse of pesticides.

Although about one-half of the samples were found to contain residues of one or more pesticide chemicals, only about 3 per cent were found to contain residues in excess of the legal tolerance or in the absence of legal tolerances the administrative guides for excessive residues. Shipments of food found to contain excessive residues are removed from the market where possible. Follow-up procedures are used to prevent other portions of a lot found to contain excessive residues from reaching the consumer.

Imported shipments of foods are sampled and examined. There are no substantial differences in residues in the foods produced in the United States and those imported from other countries.

Although approximately one-half of the samples analysed contain residues, a majority of the residues are at very low levels. Over 75 per cent of the individual residues found were 0.10 ppm or less and 95 per cent of the residues were 0.50 ppm or less. This general pattern of residue levels is observed when the data are considered by specific pesticide chemical, food category, domestic or imported products or on an annual basis. In general, foods sampled under surveillance and compliance programmes undergo further processing or preparation prior to consumption; this processing generally lowers the residue level still further.



ANNEX I

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ANNEX 2

CODEX STANDARDS PART 1

Procedure for the elaboration of world-wide codex standards

Step 1

The Commission decides on the elaboration of a world-wide *Codex Standard* and decides which subsidiary body or other body should undertake the work.

Step 2

The subsidiary body or other body so designated prepares a *proposed draft provisional standard*, taking into account the work accomplished by the appropriate international organizations. The draft is sent to the Commission's Secretariat by the Chairman of the subsidiary body or other body.

Step 3

The *proposed draft provisional standard* is sent by the Commission's Secretariat to Member States and Associate Members of FAO and WHO and to the international organizations concerned in order to obtain their comments.

Step 4

The Commission's Secretariat sends the comments received from governments and from the international organizations concerned to the subsidiary body or other body concerned, which has the power to consider such comments and to amend the *proposed draft provisional standard*, if appropriate.

Step 5

The *proposed draft provisional standard* is submitted through the Secretariat to the Commission with a view to its adoption as a *draft provisional standard*. The Commission may, however, refer it to a special subsidiary body, set up under Rule IX. 1(a) of the Rules of Procedure, before adopting it as a *draft provisional standard* or may entrust the special subsidiary body with the responsibility for undertaking Steps 5, 7 and 8 of this Procedure or any part thereof.

Step 6

The *draft provisional standard* is sent by the Commission's Secretariat for comment to all Member States and Associate Members of FAO and WHO and to the international organizations concerned.

Step 7

The comments received from governments and from the international organizations concerned are sent by the Secretariat to the subsidiary body or other body concerned, which has the power to consider such comments and amend the *draft provisional standard*, if appropriate.

Step 8

The *draft provisional standard* is submitted through the Secretariat to the Commission with a view to adoption as a *provisional standard*.

Step 9

The *provisional standard* as adopted is sent to all Member States and Associate Members of FAO and WHO and to the international organizations concerned. Members of the Commission notify the Secretariat of their formal acceptance of the *provisional standard.*

Step 10

The provisional standard will be printed in the Codex Alimentarius as a worldwide *Codex Standard* when the Commission determines that a sufficient number of Members have formally accepted it.

CODEX STANDARDS PART 2

Procedure for the elaboration of regional codex standards

Step 1

On the proposal of the majority of Members belonging to a given region submitted at a session of the Codex Alimentarius Commission, the Commission decides on the elaboration of a Codex Standard for the region concerned and decides which subsidiary body or other body should undertake the work.

Step 2

The subsidiary body or other so designated prepares a *proposed draft provisional standard,* taking into account the work accomplished by the appropriate international organizations. The draft is sent to the Commission's Secretariat by the Co-ordinator for the region concerned if a Co-ordinator has been appointed; if no Co-ordinator has been appointed, the draft is sent by the Chairman of the subsidiary body or other body.

Step 3

The *proposed draft provisional standard* is sent by the Commission's Secretariat to Member States and Associate Members of FAO and WHO and to the international organizations concerned in order to obtain their comments.

Step 4

If the Commission has appointed a Co-ordinating Committee for the region concerned, the comments received from governments and from the international organizations concerned are sent by the Secretariat to that Committee, which has the power to consider such comments and amend the *proposed draft provisional standard,* if appropriate.[1] If a Co-ordinating Committee has not been appointed, the Secretariat sends the comments received from governments and from the international organizations concerned to the subsidiary body or other body concerned, which has the power to consider such comments and to amend the *proposed draft provisional standard,* if appropriate.

Step 5

The *proposed draft provisional standard* is submitted through the Secretariat to the Commission with a view to adoption as a *draft provisional standard* for the region concerned. At the appropriate session of the Commission, all Members may present their comments, take part in the debate and propose amendments but only the majority of the Members of the region concerned can decide to amend and adopt the draft.

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[1] The meeting of the Co-ordination Committee could take place immediately before or during the session of the Commission.

Step 6

The *draft provisional standard* for the region concerned is sent by the Commission's Secretariat for comment to all Member States and Associate Members of FAO and WHO and to the international organizations concerned.

Step 7

If the Commission has appointed a Co-ordinating Committee for the region concerned, the comments received from governments and from the international organizations concerned are sent by the Secretariat to that Committee which has the power to consider such comments and amend the *draft provisional standard*, if appropriate. If a Co-ordinating Committee has not been appointed, the Secretariat sends the comments received from governments and from the international organizations concerned to the subsidiary body or other body concerned, which has the power to consider such comments and to amend the *draft provisional standard*, if appropriate.

Step 8

The *draft provisional standard* is submitted through the Secretariat to the Commission with a view to adoption as a provisional standard for the region concerned. At the appropriate session of the Commission, all Members may present their comments, take part in the debate and propose amendments but only the majority of Members of the region concerned can decide to amend and adopt the draft.

Step 9

The *provisional standard* as adopted is sent to all Member States and Associate Members of FAO and WHO and to the international organizations concerned. The Members of the region concerned notify the Commission's Secretariat of their formal acceptance of the provisional standard; other Members of the Commission may likewise notify the Secretariat of their formal acceptance of the *provisional standard* or of any other measures they propose to adopt with respect thereto, and also submit any observations as to its application.

Step 10

The *provisional standard* will be printed in the Codex Alimentarius as a *Codex Standard* for the region concerned when the Commission determines that a sufficient number of Members of that region have formally accepted it.

Step 11

The *Codex Standard* may be printed in the Codex Alimentarius as a world-wide *Codex Standard* when the Commission determines that a sufficient number of Members have formally accepted it.

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