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SAFE USE OF PESTICIDES in FOOD PRODUCTION

A Report
of the
NRC. Food Protection Committee

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This report was prepared by the Pesticides Subcommittee of the Food Protection Committee with the cooperation of the Toxicology Subcommittee in preparing sections dealing with toxicity and hazards. It is meant to replace sections dealing with pesticides in the Food Protection Committee report of December 1952, "Safe Use of Chemical Additives in Foods," which is out of print.

SAFE USE OF PESTICIDES IN FOOD PRODUCTION

The pests of crops and livestock are controlled better today than was considered possible only a decade ago. This has been accomplished primarily through use of newly developed pesticides. Many of these new materials are synthetic organic compounds, in contrast to the inorganic compounds and sulfur used predominantly prior to 1940.

The use of pesticides in the United States has increased four-fold in the past 20 years. Production of active ingredients, exclusive of diluents, carriers, and conditioning agents used in formulation, was about 215 million pounds in 1935. By 1944 the amount had increased to 513 million pounds and by 1952 to 1,025 million. In 1954, the production of organic pesticides alone had reached 419 million pounds. The organic insecticide produced in largest volume was DDT, of which 97 million pounds was manufactured.

At least 25 new materials found major markets during this era of expansion. These materials were developed because they had the ability to destroy, prevent, repel, or mitigate the activity of insects, weeds, fungi, nematodes, rodents, or bacteria. It is reasonable to assume that biologically active materials such as these might be harmful to domestic animals and man if consumed in appreciable quantities.

Many people became concerned over the possible public health problems associated with this situation in which many new biologically active materials were being introduced and rapidly finding widespread application. The Food Protection Committee of the National Research Council undertook a study of the situation in 1951 and published a general review of the problems involved and the principles that should be considered in developing new pesticides ("Safe Use of Chemical Additives in Foods." National Academy of Sciences, Washington, D. C., December 1952). Many of the basic principles set forth in that report were recognized in the drafting of Public Law 518, the 1954 amendment of the Food, Drug, and Cosmetic Act of 1938.

The time has come to review the subject again, in light of existing laws, to see what hazards are involved in use of pesticides, the procedures used in developing new pesticides, and how the legal machinery operates to safeguard our food supplies.

WHY DEVELOP NEW PESTICIDES?

Even the most ardent advocate of using chemicals to control pests on food crops would admit that they should be used only when other practical means of control are not available. However, it is recognized that use of chemicals will have to be continued and even expanded and that additional materials must be developed if crops are to be adequately protected. It is well to examine this position before discussing the safeguards that are being used.

Plants in North America are attacked by about 3000 species of insects and as many plant disease agents. The destruction caused by these pests has increased as crop culture has been intensified and land repeatedly sown to similar crops, and as varieties have been bred to genetically pure lines to increase productivity. The apple, for example, is exposed to attack by about 100 insects and a similar number of disease-causing

organisms. The severity of their attack varies from season to season and in the various geographical areas where the apple is grown, but at least 20 of the pests are a constant menace. The orchardist must, therefore, protect the crop regularly if he is to produce marketable fruit.

As is generally known, unsprayed apple and peach trees bear fruit but the yield is poor. Most of the fruit set on such trees falls before it ripens and that which matures is so scabby and wormy that little of it is acceptable for human consumption. Some persons may prefer to eat a scabby apple or a wormy peach rather than one protected by chemical treatment. This choice may be available to the suburbanite with a few trees in his backyard, but it is denied the general population. The orchardist can neither produce enough fruit to supply the population adequately nor maintain quality sufficiently high that fruit will be purchased or, under existing regulations, permitted in interstate commerce if pests are left uncontrolled.

It seems evident that the American people cannot be fed adequately unless crops and livestock are protected from insects and other pests. Although great effort has been made to lessen pest damage by mechanical means, changing crop culture, and breeding of new crop varieties, farmers have been forced in recent years to rely more and more upon chemicals for pest control.

No one knows exactly what would happen if use of pesticidal chemicals on the farm should be abandoned, but it is safe to say that we could not commercially produce apples, peaches, potatoes, citrus, and tomatoes, to mention only a few crops; and yields of many others would be drastically reduced. As an illustration, one might examine what happened to the the tomato crop in the eastern United States in 1946 when it was not being sprayed with fungicides. The late blight fungus swept up the eastern seaboard, destroying over 50 per cent of the crop in ten states and causing a loss of at least 25 million dollars. Tomato yields in Pennsylvania, for example, dropped from 5.4 to 2.7 tons per acre and the farmers were so discouraged that tomato culture declined from 34,200 acres to 19,400 acres in two years. A comparable situation developed in the Midwest when millions of acres of sweet corn were jeopardized by the European corn borer during the period 1940-1945, and sweet corn production was abandoned in many areas. Only the development of suitable spray programs for tomatoes and corn restored the crops to an economically sound basis in these two areas.

The agricultural economy suffers heavily from pests in spite of all the control measures now employed. Estimates of crop losses vary, but estimates released by the U. S. Department of Agriculture in 1954 placed the annual loss from plant diseases at 2.8 billion dollars, from insects at 2.0 billions, and from weeds and mechanical damage at 2.4 billions. This amounts to about 20 per cent of the production of our farms. In order to offset this loss on the farm an extra 88 million acres must be cultivated. Loss subsequent to harvest equals the product of 32 million acres; much of this loss is caused by pests.

Obviously, there is need for continued improvement in pest control practices. The search for better pesticides must go on. The agriculturists and their technical advisers should have available a wide range of materials to help in their battle against crop pests and diseases. The pest control specialists must have access to the largest possible assortment

of chemicals so that they may prescribe specific treatments to fit specific conditions.

The time is past when agriculture can produce efficiently with only a few pest control materials such as sulfur, copper salts, nicotine, and arsenicals. Today about 100 active materials are being used in the preparation of over 40,000 trade brand pesticides currently registered with the Pesticide Registration Section of the Department of Agriculture. Even this relatively large number of active materials is not entirely adequate because of the multitude of pests to be controlled, the ability of certain species of pests to acquire resistance to particular chemicals, the necessity of substitution when infestation occurs immediately before harvest, and the extremely variable conditions of weather and climate under which the materials must be used.

The public welfare demands that two things be done. Every effort must be made to encourage the development of better pesticides, and every possible precaution must be taken to see that they are prepared and used in such a fashion that the public will not be exposed to unnecessary hazard. The two requirements are not at all incompatible, and gratifying progress is being made in both directions.

THE HAZARD FROM PESTICIDES

Most pesticides have some toxic properties, but this does not necessarily mean that their use will create a hazard to public health. Toxicity and hazard are not synonymous terms. *Toxicity* is the capacity of a substance to produce injury; *hazard* is the probability that injury will result from the use of the substance in the quantity and manner proposed. For example, the most toxic material will not present a food hazard if it evaporates or becomes nontoxic by decomposition before the crop is used for food.

In any attempt to evaluate hazard, one must distinguish between use or operational hazards involved in applying pesticides and the hazards involved in food contamination. In general, *operational hazards* are related to the acute and subacute toxicity of the pesticide and may be estimated from the relative toxicity of the material and the degree of exposure to it. The user must be fully informed through proper labeling and adequate instructions regarding the hazards involved. He should then be at liberty to make a free choice from the materials available and assume full responsibility for his actions.

Every effort should be made to reduce operational hazards to a minimum. That such efforts are effective may be reflected in the fact that farm accidents involving pesticidal chemicals are insignificant in number when compared with farm accidents from use of mechanical tools.

Food hazard is, in general, closely related to chronic toxicity of the pesticide. Chronic toxicity is estimated from biological changes in animals exposed to the intake of small doses of a material over a protracted period. If the minimum dose of a pesticide causing chronic effects is known, hazard can be estimated from the amount of residue remaining on or in food reaching the consumer.

The inherent toxicity of a pesticide to warm-blooded animals may have little or no direct bearing on the final food hazard. Many of the more toxic materials are applied at times when the edible portion of the crop is not exposed. As a rule, such chemicals are applied in proportionately smaller amounts than are less toxic materials, and frequently

the more toxic compounds are quickly destroyed through chemical change or lost through decomposition or evaporation.

The magnitude of the residue on edible portions of the crop must be determined before hazard can be estimated. The factors influencing amount of residue may be summarized as follows:

1. Rate of application, i.e., magnitude of initial deposit
2. Time of application relative to:
   a. Development of edible plant parts
   b. Exposure of edible parts to treatment
   c. Time elapsed between last application and crop harvest
3. Rate of loss of a pesticide deposit from the plant
   a. Rate of decomposition or degradation of active ingredient as affected by:
      (1) Fluctuations in temperature, moisture, sunlight
      (2) Plant secretions
   b. Rate of evaporation of volatile materials as affected by environmental conditions
   c. Rate of erosion of residual deposits as affected by:
      (1) Rainfall
      (2) Wind
4. Dilution due to growth of plant
5. Adherence to or absorption by plant parts
6. Efficiency of residue removal methods and extent of their use
7. Miscellaneous practices in application
   a. Effect of changes in formulation on any of the listed factors
   b. Number of applications and, particularly, the date of last application

THE PROCESS OF DISCOVERING AND DEVELOPING A SAFE PESTICIDE

Chemicals for use in agricultural pest control are discovered by extensive testing of materials from four sources:

1. Inorganic compounds usually containing a metal or sulfur but no carbon or nitrogen
2. Synthetic organic compounds containing carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, and the halogens in various combinations of two or more elements
3. Antibiotics produced by molds or bacteria. These are organic chemicals, usually of complex composition.
4. Products of higher plants

Several years have elapsed since a major new pesticide from higher plants has been introduced into commercial usage. The antibiotics have just begun to be used, and few are on the market for use as pesticides. The inorganic pesticides dominated the field from 1880 to 1940, but practically no new ones are being proposed for use at this time.

The use of synthetic organic pesticides has grown continuously since their usefulness was established in the period 1934-1942. Almost limitless possibilities are available in developing new types of organic chemicals. Many classes of compounds are available to work upon, and the chemist can modify the chemicals so that they will have subtle differences in biological activity. It may be possible, therefore, to develop additional useful fungicides, insecticides, nematocides, and herbicides by accentuating their ability to kill plant pests and by suppressing the tendency to kill or injure the crop. It is likely that extensive ex-

ploration of the field of organic chemistry for safer, more effective pesticides will go on for several decades. These are the chemicals that dominate our thinking as we try to formulate policies for encouraging the orderly development and safe use of agricultural chemicals.

Several companies ordinarily test 1000 to 3000 new organic compounds for pesticidal properties each year. By the best estimates available only about one of each 2000 candidates proves to be commercially acceptable. By the time one successful compound is conceived of by a chemist, evaluated by a biologist, synthesized commercially by chemical engineers, evaluated for field performance by industry and public agencies, certified for activity by government, and shown to be safe for use, a bill of one to two million dollars may have been incurred. This includes not only the actual cost of the one successful compound but also the costs incurred by all the failures encountered.

The items of cost vary widely for different compounds, but reasonable estimates for various items are about as follows. The cost of synthesizing each compound will be $350 to $500. A series of thorough laboratory and greenhouse tests made upon it will cost some $200 to $350. The more promising survivors will have to be subjected to small-scale, replicated field trials for the particular use under consideration. Each such test involving comparisons with standard commercial products will cost $500 to $2000. The test must be repeated at least once in the season and in two geographic areas before an adequate appraisal can be assured. Since local weather and other crop production conditions may frequently defeat the purpose of the test, many tests must be repeated.

If the material survives the small-plot tests, its sponsor may then consult research specialists in the state experiment stations, the U. S. Department of Agriculture, and elsewhere on the potential usefulness of such a material. He may provide them with samples for study in relation to problems peculiar to their geographical regions. The production of these experimental quantities of the material and the collection and interpretation of data from perhaps scores of collaborators will cost $3000 to $40,000. If the collaborative testing extends over several years, the cost will be much higher than indicated. This investment provides the sponsor with data confirming or contradicting his own observations, data on a wide variety of pests to determine the scope of usefulness of the material, and observations on the effect of local climate and soil conditions on its performance and safety.

Before the sponsor of a chemical enters into this collaborative period with state and federal agencies he must make certain policy decisions and commitments. First, he must decide whether the material has a chance of competing with other pesticides on the market. If it is likely to be too expensive at the dosage indicated in his preliminary trials as necessary for pest control, he must abandon it or delay field research until he has found a cheaper method of manufacturing it. Second, he must begin research on process development. This will cost $10,000 to $500,000, depending upon the complexity of the molecule and the physical conditions necessary to synthesize it and purify the final product. Third, he must develop analytical methods to check the purity of the pesticide in the factory and to determine residues in or on foods. Often the residue method will have to be sensitive to as little as 0.02 parts per million in or on a product. A cost of $1000 to $25,000 may be anticipated. Fourth, he

must initiate studies on toxicology. These will cost about $3000 in the preliminary stages and will extend to $30,000 to $50,000 if the entire battery of tests is completed.

It is obvious that the policy decisions at this point are difficult because of the magnitude of the expenditures involved and the many intangible factors that lie ahead and cannot be appraised. Usually a stepwise program of research is started simultaneously on field performance, process development, analytical methods, and toxicology in such a manner that the entire program can be abandoned or accelerated as indicated by available information.

The initial toxicology tests should be made as early as possible and before a chemical is placed in pilot plant or factory production or is given to outside collaborators. The initial program consists of dermatological tests, first on animals then on human subjects, and acute toxicity tests on animals to determine the minimum lethal dosage by mouth. These two tests will indicate whether extreme hazards are likely to be involved in routine field trials on small plots. Further knowledge of toxicity is not necessary at this time, since all produce from the plots will be discarded or used for laboratory testing for residues and none will be used for human food or livestock feed. After extensive small-plot field trials have indicated that a material is an effective pesticide and may be commercially developed, it should be subjected to feeding tests on animals to determine subacute and chronic toxicity.

While the chronic toxicity tests are in progress, analytical procedures must be perfected and data obtained on residues remaining in or on the edible portions of various crops at harvest time. It is expected that residue data will be obtained for plants treated so as to control the pest under representative conditions.

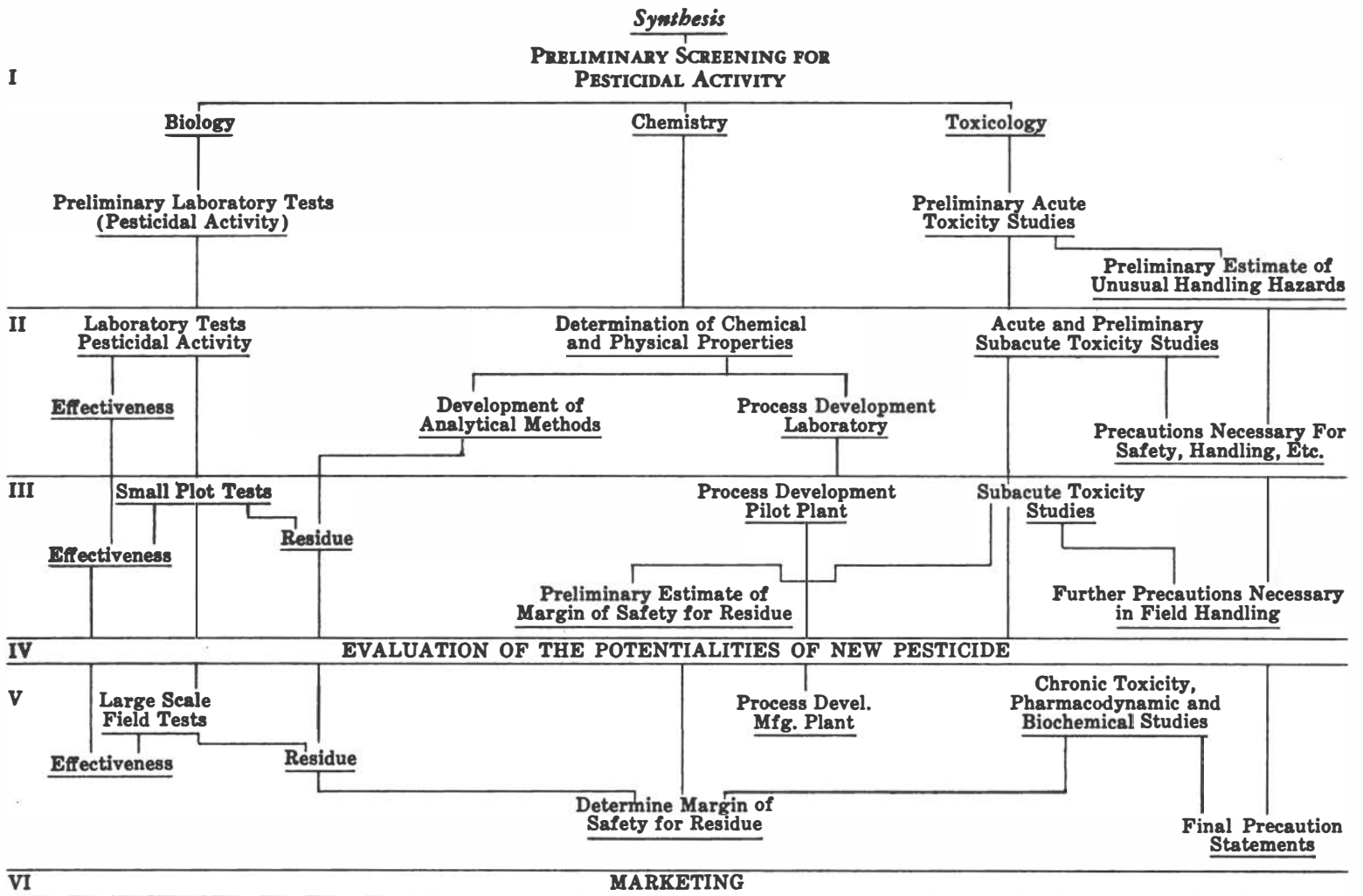
At the end of this period of evaluation, sufficient data may be available to warrant initiating large-scale field trials on representative farms and to place the new product in the hands of a few farmers in each of several localities for their appraisal. In this intermediate stage of product development, testing under farm conditions is absolutely essential for detecting any flaws that would prohibit the practical use of the product. Since in these tests the product will be used on marketable crops, it must first be approved for this use by the regulatory agencies. A limited license for experimental use may be granted at this time if adequate data are available to assure the responsible officials that the material is safe and sufficiently promising to warrant extensive trials. However, more residue data from the proposed field trials may be required before release of the material for unrestricted commercial use is approved. This exploratory period provides an opportunity under closely supervised conditions to perfect the use of the product and assure its safety.

The series of steps described above may be summarized graphically as occurring in six stages according to the scheme shown on the following page.

DATA REQUIRED BEFORE MARKETING A NEW PESTICIDE

The manufacturer of a new pesticide and the appropriate regulatory agencies must assume certain responsibilities to the public when the pesticide is placed in commercial use. Government has the responsibility of safeguarding public health and of protecting the public from fraud. It establishes maximum residue tolerances for materials that may present a hazard to the public if excessive amounts occur on food commodities and

STAGES IN THE DEVELOPMENT OF A NEW PESTICIDE



enforces compliance with them. It also requires assurance that the material is effective for the use proposed. The manufacturer must assume, in addition to his responsibility with respect to public health, the usual responsibility for performance of the product as claimed. He should be granted reasonable freedom to incur well calculated risks pertaining to crop damage and performance of the material as a pesticide.

The effectiveness and safety of a new pesticide, when it is used in the proposed manner for the specified purpose, must be clearly established before the pesticide is marketed. The chemical and physical properties and the function of the proposed pesticide, its toxicity, both acute and chronic, and time and method of application will determine the amount of information required to establish adequately its effectiveness and relative safety. Data on important points should be of such nature and magnitude as to be reasonably conclusive.

The following proposals are presented as both practical and adequate requirements for the pre-marketing evaluation of a new agricultural pesticide. Many chemicals may have very restricted uses or for other reasons may not require or warrant the thorough investigation indicated by all proposals listed. The requirements for evaluation can be restricted in accordance with proposed uses of the product.

I. Chemical and Physical Data

Information in conformance with the following should be as complete as possible and should pertain to the commercial or chemically pure grade of the pesticidal chemical and not to formulations thereof.

A. Chemical name and strucutural formula. Trade names, abbreviations, code numbers, and any other designations used to identify the compound in the literature and elsewhere, should be cited.

B. Degree of purity of the pesticidal chemical product, with statement of any materials other than the principal active ingredient known to be present in the commercial grade material.

C. Physical and chemical properties which may affect use or acceptability, e.g., flash point, freezing point, inflammability, taste, odor, color, etc.

D. Solubility in water and other solvents. Data on solubility in oils, fats, waxes, organic solvents, and body fluids are important.

E. Melting and/or boiling point.

F. Vapor pressure at 25° C. and over the temperature range of use.

G. Other physical and chemical identifying characteristics, including particularly spectra and refractive index. These characteristics are especially necessary if the pesticide is not a pure chemical compound.

H. Stability and reactivity. Information on rate of decomposition before and after application, compatibility with other pesticides, and other reactions of interest to the user, such as corrosion of equipment, reaction with hard water, etc., is important.

I. Suggested analytical methods for macro- and micro-quantities of the active ingredients, including methods of extraction from plant and animal tissues.

J. Methods of removal and decontamination by physical or chemical procedures of residual quantities of the pesticide remaining on crops.

II. Biological or Use Data

Pesticidal effectiveness should be established in terms of percentage reduc-

tion or control of pests, increase in yield or quality of crop, or other economic gain or practical benefit following application of the specified pesticide under the conditions prescribed, compared with results from standard treatments and/or untreated controls. Examples of economic gains or practical benefits other than pest control are: economy or ease of production, harvest, or storage of the crop; flexibility in time of planting or harvest, even at the possible sacrifice of yield; and general benefit to livestock, plants, or human welfare not necessarily related to yield.

A. Establishment of pesticidal effectiveness

1. *Laboratory tests.* The results of laboratory tests for the effectiveness of the product against the pest in question and related species should be made available. Considerable weight should be placed on such tests from the standpoint of the measurements of pest response. Characteristics of the product and its proposed use will largely determine the suitability of such data as a principal basis for evaluations.

2. *Small-plot tests.* The amount of data obtained in small-plot tests should be adequate to demonstrate performance under natural conditions. The proposed use, the nature of the pesticide, the method of application, and the amount and consistency of the data will determine the weight to be given such evidence in the evaluation of a product. Data pertaining to specified uses should be based on tests conducted for at least one growing season under environmental conditions similar to those prevailing in the area where use of the material is proposed.

3. *Large-scale field tests.* These should be made on farms, using commercial-type equipment under farm conditions. The data obtained in such tests are considered the most reliable indications of how the material may be expected to perform in practice. Depending upon circumstances and conditions, data from laboratory and small-scale field tests may replace or supplement field test data.

4. *Supplemental information.* Supplemental information accompanying experimental data should provide a comprehensive description of the material and its use and should include the following points where applicable:

   a. Names and percentages of active ingredients and such additional information as is necessary for proper evaluation for ultimate commercial use. The public declaration of so-called "trade secrets" as to methods of formulation and minor adjuvant ingredients should not be considered essential.
   b. Extent of dilution for use
   c. Rates of application (per acre, per animal, etc.)
   d. Methods of application
   e. Pests controlled, prevented, or repelled, or other benefits
   f. Dates of treatment and dates when results were taken
   g. Description and identity of plants or animals treated, together with a statement of their approximate development, age, or size when tests were started and when completed
   h. Identity of application areas and description thereof if neith-

er food plants nor animals were treated (barns, ornamentals, etc.)

i. Geographical site of the tests

j. Identity of persons and organizations conducting the tests

k. Results in detail, with information as to the immediate and delayed effects and pertinent data on environmental conditions prevailing during the test period

B. Safety for plants and animals

1. *Plants.* Data on plant injury should be collected in connection with the performance tests. If injury occurs, careful notation should be made of the type of injury, e.g., stunting, reduced yield, leaf drop, tip burn, spotting of the leaves, etc. Where plant injury seems probable, appropriate warnings should be made available.

2. *Animals.* If the pesticide is proposed for use on animals, data should be obtained on its irritant or other injurious properties.

C. Compatibility

Data on compatibility with other materials are desirable and should be provided where such materials would obviously be used in the same spray schedule in accordance with recognized practices.

D. Reduction in quality of food

In connection with the performance tests, observations should be made for any departure from the normal in flavor or appearance which may affect the acceptability of food items.

E. Accumulation in soils

As a part of the performance tests, observations should be made to determine whether the pesticide is stable and tending to accumulate or unstable and transitory in soils. Observations from laboratory, greenhouse, or small-plot tests will generally be adequate.

F. Residues

Data should be obtained on the amount of residue remaining on or in foods at harvest under the proposed method of treatment. The amount of such data required will depend upon (1) the recommended use, dosage, and time of application of the pesticide; (2) the acute and chronic toxicity of the chemical; (3) its physical and chemical properties; and (4) its rate of disappearance.

If pesticide residues may be anticipated on or in the food product at the time of harvest or slaughter, residue data should be established indicating the residue likely to remain after effective dosages of the pesticide have been made under optimum conditions for retention and over the maximum time period of application. These data, which may be obtained by analyzing representative crop material harvested from the tests on pesticidal effectiveness, should show the total amount of chemical found on and/or in a stated weight of the food product.

Fewer residue data will be required for pesticides that are not toxic to warm-blooded animals at recommended use levels, are highly volatile or otherwise non-residual, or are decomposed to nontoxic components before harvest.

If a potential hazard is disclosed by the preliminary data on the amount of residue or the toxicity of the compound, more extensive data on the magnitude of residues remaining at harvest on representative food crops produced under representative environmental conditions should be obtained.

Either chemical or bioassay methods of demonstrated reliability may be used for residue determinations.

Methods for removal of excessive residues should be developed.

G. Operational hazards

Proper precautionary procedures relative to handling and use should be developed.

III. Toxicologic Data

Many of the pesticides are known to be toxic to warm-blooded animals. Data are needed to provide for: first, a clear understanding of the toxicity of the compound; second, an assessment of the hazard to consumers created by use of the compound to meet specific pesticidal needs; and third, an estimate of the hazard to those who must handle the material in manufacturing, formulation, crop testing, and application.

In studies of toxicity, special attention should be given to: (1) uniformity of response within and among species; (2) rate, extent, and mode of detoxification and elimination; (3) tendency toward accumulation in the body; (4) occurrence of unusual or alarming reactions such as carcinogenesis; (5) occurrence of sensitivity, tolerance, or idiosyncrasy in response to the compound; (6) the possibility of synergistic action; and (7) the possibility of degradation of the compound before ingestion to a substance more toxic than the original.

Toxicity must be established in terms of generally accepted indices of injury such as structural, biochemical, and physiologic changes in specific organs or body systems. Toxicity testing is often guided by a knowledge of the chemical or physical properties of the substance at hand and of the effect of substances of similar properties or structure. Tests should be so designed as to emphasize any suspected potential of the substance for injury in order to give as stringent a test as possible. Such considerations may influence the choice of a test animal in order to obtain information in the most sensitive species.

The dosage levels investigated should range from an absence of the pesticide in controls through a series of intermediate levels and through at least one producing significant effects. The material should be fed at a sufficient number of levels to determine the maximum level of no response and to indicate the nature of the response at the higher levels. These observations will allow an estimate of safety in the species under study and will serve as a basis for extrapolation to the other species. In growth studies, differences may not be interpretable unless caloric intakes are equalized or otherwise taken into account.

It is not possible to design a single program that will apply to every pesticide in all its applications. As an investigation progresses, data obtained may indicate the advisability of altering the program of study as originally designed.

With the above considerations in mind, the following tests are suggested as a program which can be reasonably expected to yield the toxicologic data needed to assess hazard:

A. Determination of toxicity

1. *Acute toxicity.* The approximate lethal single oral dose should be determined in at least three species, at least one of which is a non-rodent such as the dog. This information is of value in planning studies of subacute or chronic toxicity and in the recognition of symptoms. Extension of these acute tests may occasionally be desirable.

As a basis for estimating operational hazards, information should be developed with respect to the irritating and sensitizing properties of the compound. Also, data concerning toxicity by percutaneous absorption and by inhalation should be obtained if there is presumptive evidence of hazard via these routes.

The signs, clinical course, gross and microscopic tissue changes, and, if possible, the mode of death should be described. Surviving animals should be observed until completely recovered.

2. *Subacute toxicity*

   a. *Oral.* Results from a 90-day feeding test with ten rats of each sex at each of several feeding levels may make possible a decision as to whether the proposed use is too hazardous to warrant further toxicologic study. The information obtained may also serve as a guide in selecting feeding levels for the chronic toxicity study. The dose-response relationship should be examined.

   The data sought may include, at each of the several feeding levels, the effects on food consumption, growth, mortality, blood and urine composition, and organs as measured by weight and histopathologic findings. Any alterations in functions and behavior should be noted. If a known physiologic or biochemical system is affected by the pesticide, periodic measurements of the cumulative effect on the system should be made. Effects on digestibility and utilization of the ration may be important.

   The subacute feeding tests with rats may be so designed that enough rats are used at each dietary level to provide animals to be continued in tests for chronic toxicity, in the event it becomes advisable to conduct such tests.

   b. *Percutaneous.* As a general rule three or more rabbits are treated at each of several dosage levels for at least three weeks. The material under study is applied periodically to a clipped area of skin, care being exercised to prevent ingestion by the animal. Observations as indicated in the preceding section are made of the animals.

3. *Chronic oral toxicity.* Long-term tests are conducted on the premise that the possible effects of the lifetime ingestion of a pesticide in food by man cannot be predicted from results of tests less stringent than lifetime feeding in a short-lived animal (approximately two years in the case of the rat) and one year or longer feeding in the dog or monkey. Obviously, these tests may be either inadequate to the purpose or more exacting than necessary, but past experience has not supplied a more rational alternative.

   In the tests with rats the material is fed at selected levels in the diet to groups of 25 or more weanling animals of each sex. The levels to be fed should be

chosen on the basis of the data obtained in the subacute feeding tests.

The two-year tests may include observations on: food consumption; growth; absorption, excretion, and tissue storage of the material; mortality; organ weights; histopathology and hematology; blood and urine chemistry; such changes in behavior and function as may be determined by gross observation; and such other effects as may be indicated in special circumstances. Effects on ration digestibility and utilization and on reproduction and lactation may be especially significant.

In the case of dogs or monkeys, the usual procedure is to feed the material under test to groups of three or more animals at three or more intake levels for one year or longer. Observations are similar to those made in the chronic feeding test with rats. The dog or monkey tests are generally started after the rat studies have been in progress long enough to provide data to aid in selecting the feeding levels likely to be most informative.

Where human exposure to the pesticide has occurred, all appropriate tests should be employed to determine whether there have been any adverse effects.

4. *Pharmacodynamic and biochemical investigations*

   a. *Pharmacodynamic.* The aim of pharmacodynamic tests is to describe the mode of action by which the compound brings about changes in functional systems. There is no succinct way of describing the extent of investigation necessary, this being variable with the systems affected and the technics available for the study of such functional effects. The program should at least provide a basis for the treatment of accidental poisoning if technically possible.

   b. *Biochemical.* These investigations should be designed to study the absorption, excretion, storage, and metabolic fate of the pesticide. The scope of the investigation will vary from compound to compound and with the intricacy of the processes. The minimal program should seek to describe the routes of absorption and excretion, the extent and sites of storage, the rate of release from depots, and the functional implications thereof. Since many pesticides exhibit their effects by inhibiting enzymatic activity and in other ways interfering with normal metabolic pathways, knowledge of the mode of action may be important.

      The influence of a pesticide upon the nutritional contribution of the foods in which it may appear must be considered. It is important to ascertain the effect of the pesticide on the stability of nutrients in the foods, as well as on the digestibility and utilization of the ration.

B. Determination of hazard

Once the toxicologic data have been assessed and the toxicity of the compound adequately described, there re-

mains the task of estimating hazard. Hazard is estimated from knowledge of toxicity and the anticipated levels and patterns of consumption.

In order to estimate the probable intake level of the additive, information on its proposed use is essential. This information includes (a) the amount of the pesticide remaining on foods, (b) the proportion of the usual diet composed of foods in which residues of the pesticide may appear, and (c) the extremes of probable intakes of these foods. From this information the maximum potential consumption by individuals or special groups as well as the average potential consumption for the general population can be estimated.

The translation of toxicologic data into terms of human use levels and margins of safety is one of the most difficult problems in the interpretation of such data. Each substance presents problems peculiar to itself and requires individual consideration by those competent to exercise objective judgment of all the available evidence. Generally the assumption is made that man is more susceptible to poisons than are the laboratory animals.

The decision as to a safe level for a pesticide residue in foods should be based upon such factors as the maximum dietary level that produced no unfavorable response in test animals, the severity of response in test animals at dietary levels above the no-response level, and the estimated potential for human consumption of the food or foods for which the additive is proposed.

LEGAL PROCESSES FOR PROTECTING THE PUBLIC

Legal restrictions on the use of pesticides in food production are provided for by the Federal Food, Drug, and Cosmetic Act of 1938 as amended in 1954 by Public Law 518 and in 1956 by Public Law 905, and the Federal Insecticide, Fungicide, and Rodenticide Act of 1947. These two acts recognize pesticides as essential to food production and provide the machinery for establishing nonhazardous tolerances and enforcing compliance with them.

Before any new pesticide can be moved in interstate commerce it must be registered with the Pesticide Regulation Section, Plant Pest Control Branch, Agricultural Research Service, USDA, under terms of the Insecticide, Fungicide, and Rodenticide Act. The registrant must present data such as those suggested in the preceding section to prove its usefulness, safety to the public when label precautions are followed, compatibility on various crops as recommended, and safety of the treated crop product for use as a livestock feed or food for human consumption. Suitable analytical procedures for identifying the material and measuring its residue on crop produce must be given the authorities.

Any labeling appearing upon the pesticide package, accompanying the pesticide at any time, or referred to on the label or in literature accompanying the pesticide must be approved and must bear suitable warnings if any use hazard is involved. When any risk of harm to the public health is anticipated from the use of the product, the Administrator of the Act confers with officials of the Public Health Service as to the accuracy of the evidence submitted to show that the warning statements are adequate, when complied with, to protect the public. In addition, when food contamination is involved, the Administrator of the Act confers with representatives of the Food and Drug Administration regarding the completeness of the toxicologic data, the accuracy of the residue

information, and the hazards involved in the amounts of residue likely to result.

Data on toxicology and residues must be submitted to the Commissioner, Food and Drug Administration, in the Department of Health, Education, and Welfare, with a petition for FDA to establish specific residue tolerances for each crop that might bear residues from the use of the pesticide as proposed. If the data presented are considered inadequate, either from the toxicologic or residue viewpoints, the Commissioner can reject the application, or can establish a tolerance of zero. Once a tolerance is published in the Federal Register it becomes operative and the Food and Drug Administration is authorized to enforce it. Any raw agricultural commodity found in interstate commerce, or at any time after it has moved in interstate commerce, with a residue exceeding the legal tolerance is subject to seizure by FDA and condemnation by court decree. Tolerances can also be enforced by criminal proceedings. Because of complexities in defining usefulness, reaching decisions on the residues remaining, or determining levels of complete safety, a large measure of personal judgment has to be exercised by the Administrators of the two Acts and their assistants. Their decisions must be based upon technical information and made solely in the public interest.

To expedite the establishment of safe tolerances, the law contains a provision for referring debatable points on maximum allowable residues to advisory committees of unbiased experts. The National Academy of Sciences selects experts to serve on the advisory committees which are appointed by the Food and Drug Administration. Such committees are composed of specialists in the subject matter of the petitions to be reviewed, and with training in such fields as medicine, pharmacology, toxicology, chemistry, biology, and agriculture.

The procedures now in force are generally considered to be definitely superior to those in use before the recent amendment of the law. Although the old procedures had protected the public, as shown by the absence of authenticated association of pesticide residues with human illness, the amendment of the law assures even greater protection to the public health and provides an orderly process for the development, approval, and use of new pesticides.

The present law makes it clear that every pesticidal chemical intended for use in the production, storage, and transportation of raw agricultural commodities must be proved safe before it is used on food crops. This responsibility rests with the sponsor of the chemical. The consumer can rest assured that every care is taken to provide foodstuffs that are wholesome and safe insofar as modern scientific procedures can be applied.

The law provides that a decision must be made promptly on accepting or rejecting a material that has been proposed for use as a pesticide. Residue tolerances must be established by the Food and Drug Administration within a specific time limit, provided data supporting the petition for a tolerance are adequate to justify the tolerance. This assures industry that research progress will not be blocked by official indecision, and that significant discoveries can be put to use as promptly as is commensurate with public safety. In case differences of opinion arise as to what constitutes a safe tolerance, a workable system is available whereby the most competent scientists in the country can be called in for advisory service, and

unresolved controversial issues can be referred to the courts.

The foregoing procedures apply to all insecticides, fungicides, rodenticides, and herbicides used in the production, storage, and transportation of raw agricultural commodities. Nematocides and growth regulants are controlled by other provisions of law. Residue tolerances of these substances are set as a result of proposals submitted by an interested person, or upon the initiative of the Department of Health, Education, and Welfare. Opportunity is given for anyone who might be adversely affected by the tolerance proposed to express his objections before the tolerance becomes effective. Proposed tolerances cannot be appealed to an advisory committee under present interpretation of the law, however.

Once safe residue tolerances are established, they can be enforced by sampling and analyzing produce as it moves in interstate commerce from the farm to the consumer. Offenders can be prosecuted and punished in court for their misuse of any material.

The foregoing discussion of legal processes is concerned only with regulation of pesticide residues on food in interstate commerce, or food held at any time after it has moved in interstate commerce—the extent of Federal control. Most of the states have comparable laws regulating the sale and use of pesticides, with which the manufacturer must comply.

The procedures established are costly to both government control agencies and the agricultural chemicals industry. This cost eventually is paid by the consumer in increased food prices and taxes. He will benefit in the long run, however, because of the greater productivity of our farms and the reduction of food losses in transit and storage.