Safe Use of Chemical Additives in Foods (1952)

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BASIC PRINCIPLES INVOLVED IN EVALUATING SAFETY IN THE USE OF CHEMICAL ADDITIVES IN FOODS

The questions posed by additives in foods require objective, unbiased study, with due consideration of many types of possible advantages and disadvantages which may accompany the use of the proposed additive. It is fundamental, however, that decisions regarding foods be aimed at providing the consumer with an adequate supply of a wholesome product with good acceptability. A wholesome food product must, among other qualities, supply at least the nutritional values which are traditionally associated with the food, and it must be safe for continuous use in the diet under all patterns of consumption which are to be expected to occur during the course of its use. Decisions emerging from such a variety of considerations must involve judgments made through understanding and interpretation of critically designed studies. The considerations are so varied as to demand group study and mature, conservative judgment.

The distinction must be made between hazard and toxicity. 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 in the manner proposed. An estimate of the hazard in relation to any substance must be based upon knowledge of the toxicity and of the details of its use.

Intentional additives should not enter foods until their safety for consumption has been established to a reasonable degree of probability, as judged by competent experts. Similarly, the safety of incidental additives must be established in terms of their occurrence in food products as marketed. While the ultimate test of complete safety is the alert observation and intelligent scrutiny

of the effects of the use of a substance in foods, the use of any new additive in foods should not be permitted until the best judgment based upon studies on animals, and where possible on man, indicate that deleterious effects will not result from its use.

Experimental studies of the physiological, pharmacological, and biochemical behavior of a proposed additive, made in various species of laboratory animals and in limited numbers of humans, can reduce to a very low degree the uncertainty of the safety of its general use.

The extent of such studies of a particular additive in food varies with several factors which determine the amount and form likely to be consumed by the human. Such considerations include:

a. Whether the additive is to reach the consumer by direct additions to food or indirectly through animals which have consumed the additive.
b. The possibilities of alteration of the additive after its addition to foodstuffs or consumption by animals.
c. The proportion of the usual diet which is composed of foods in which the additive may appear.
d. The extent of the presence of chemically or pharmacologically similar substances already in the usual diet.
e. The amount of the additive which it is technically desirable to add to foods, or the amount which will enter foods incidental to the main purpose of the use of the substance.
f. The nature and degree of adverse effect which the additive may produce and the class of persons which may be affected by it.
g. The ease with which persons may avoid foods containing the additive.
h. The degree of temptation to excessive use of the additive.
i. The possibility or ease of regulatory control of the use of the additive.

j. The technological justification, or the necessity, for the use of the additive.
k. The influence of the additive upon the nutritional contribution of the foodstuff in which it may appear.

It is important in the interpretation of the toxicological studies that qualitative factors be given due consideration, including:

a. Uniformity of response within and among species.
b. Ease and mode of detoxication, and tendency toward accumulation in the body.
c. Occurrence of unusually alarming reactions such as carcinogenesis.
d. The occurrence of sensitivity, tolerance, or idiosyncrasy in response to use of the compound.

Whenever, in the light of the principles set forth above, methods are needed for the collection of toxicologic data, those set forth by Lehman, et al. (Procedures for the Appraisal of the Toxicity of Chemicals in Foods; Food, Drug and Cosmetic Law Quarterly, September, 1949) appear *pro tem* to be best suited to the purpose.

BASIC CONSIDERATIONS INVOLVED IN EVALUATING HAZARDS ENCOUNTERED IN THE USE OF PESTICIDES ON FOODS

Maintenance of the present nutritional status of the American public is contingent upon the continued production of an adequate food supply. Plant and animal pests rank among the foremost causes of food destruction, food deterioration, and food contamination. Hence the necessity of protecting growing crops and produce from serious attack by insects, plant diseases, and other pests is quite obvious to all concerned. In recent years science has placed in the hands of the farmer, the food handler, and the food processor many valuable chemical tools or weapons to aid them in their unending war with pests of all types. These chemical tools are commonly referred to as pesticides.

Definitions. Pesticide was defined by the late Dr. S. A. Rohwer as "a product, substance, or mixture of substances — gaseous, liquid, or solid — which may be used to destroy, prevent, control, repel, or mitigate any form of plant or animal life or viruses (except viruses, fungi, or bacteria on or in living man and other animals), and weeds." The term pesticide thus embraces such terms as insecticide, fungicide, herbicide, acaricide, and rodenticide, and their various subdivisions. A pesticide may be a single chemical substance or it may be a mixture of two or more substances prepared in a suitable formulation. Where mixtures are involved, the ingredients included to perform the primary function of a pesticide are properly referred to as pesticidal chemicals, and the other components of the mixture are classed as carriers or adjuvants.

The various classes of pesticides — insecticides, fungicides, etc. — and their various component parts may be similarly defined.

Necessity for Using Pesticides. At least 3,000 species of insects and twice as many disease agents attack crops. Some of these destroy plants outright while others reduce the yield by 10 per cent or more and impair the quality of produce. Apple growers, for example, must protect the crop from about 100 insect pests and 200 infectious diseases. The damage by these plant and animal pests can be and is reduced somewhat by mechanical, ecological, and biological control methods, but such methods are wholly inadequate to obtain effective control.

There is abundant evidence that our fruit, vegetable, and many other staple crops cannot be produced economically, efficiently, and in an adequate volume without chemical protection from insects, plant diseases, weeds, and other pests. Uninhibited insects and plant diseases would largely eliminate the commercial production of such crops as apples, peaches, citrus fruits, tomatoes, and potatoes, to mention only a few, and would drastically curtail the production of many other major crops, thereby jeopardizing our agricultural economy and an adequate food supply for the American public.

Some might conceivably prefer to eat a scabby apple or a wormy peach rather than a chemically treated fruit. That choice might be available to the suburbanite with a fruit tree in his back yard, but there is considerable evidence to show that it would not long be available to the average American consumer if the use of pesticides were abandoned or prohibited. For example, it is well known that apple and peach orchards will continue to produce fruit after they have been abandoned, but most of it falls to the ground prematurely, and practically all of that which remains could not pass market grade inspection and could not be shipped or sold.

Need for a Wide Choice of Pesticides. Time was when the entomologists and the plant pathologists were called upon to do the best they could with a few pesticidal chemicals such as sulfur,

copper salt, a few arsenicals, and nicotine. Today, approximately 100 pesticidal chemicals are in use or available for use, and over 30,000 pesticide formulations have been registered for labeling and use by the Insecticide Division of the U. S. Department of Agriculture.

Each pesticidal chemical and each pesticide has its distinct advantages, disadvantages, and special uses. Therefore, just as the physician and the pharmacist require a generous assortment of pharmaceuticals for the compounding of prescriptions, so, too, the agriculturist and the pesticide dealer should have ready access to the largest possible assortment of chemicals so that they may likewise prescribe specific treatments to fit specific conditions. Many new pesticides have been developed which are more effective for specific purposes than are the materials previously used for those same purposes. The use of these new chemicals in argriculture parallels developments in the field of medicine where sulfa drugs and the new antibiotics are now frequently recommended and used in the place of the less efficient drugs which were in common use a few years ago.

Hazards Involved in the Use of Pesticides. Most pesticides have some toxic properties. If they did not have these properties they undoubtedly would not control pests and therefore would not be pesticides. Toxicity and hazard obviously 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 in the manner proposed. In evaluating the hazards involved in the use of pesticides, one must distinguish between use or operational hazards and the hazards involved in food contamination.

In general, use hazards are related to acute toxicity and may be measured in terms of the relative acute toxicity of the pesticide and the degree of exposure to it. The user should be

fully informed through proper labeling and adequate instruction 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. All accidents are deplorable and every reasonable effort should be made to reduce the operational hazard to a minimum; however, it should be recognized that farm accidents involving the use of pesticides and other chemical tools are insignificant when compared to farm accidents involving the use of mechanical tools. (Operational hazards are related to but are outside the scope of the Food Protection Committee's activities. These are being studied by the American Medical Association and other groups.)

Food hazards are, in general, closely related to the chronic toxicity of the pesticidal chemical involved and may be measured in terms of the chronic toxicity of the chemical and the amount of residue remaining on or in food reaching the consumer.

The inherent toxicity of a pesticide or pesticidal chemical 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 short-lived. In other words, they may be quickly destroyed through chemical change or lost through decomposition or evaporation. It would not, therefore, be in the public interest to unduly restrict the use of these valuable pesticides strictly on the basis of their inherent toxicity to warm-blooded animals. Fruit and vegetable growers should not be denied the right to use a pesticidal chemical, no matter how poisonous, provided its use as recommended does not present a hazard to plant life, individuals, or the public health.

Factors that Determine the Presence or Absence of Food Hazards. Although several factors are involved, two are outstanding in de-

termining the magnitude of any possible or probable food hazard that may develop where pesticides are used in the production and processing of food products:

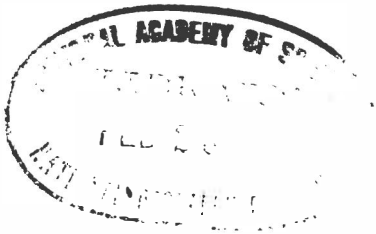
1. The inherent toxicity of the pesticidal chemicals used.
   A. The acute toxicity of the substance will be rarely involved.
   B. The chronic toxicity, which is a measure of adverse effects resulting from prolonged ingestion of small amounts of a deleterious substance, will be an important consideration.
2. The magnitude of the residue — in other words, the actual amount of the pesticidal chemical remaining on or in the food when it reaches the market or is ready for consumption.

Factors that Will Determine the Magnitude of a Pesticide Residue. Pesticides will vary greatly in their physical properties and their application may vary greatly as to time, method, and amount. The presence or absence of a chemical residue at harvest time, therefore, will be determined by a number of factors entirely independent of the toxicity of the chemical itself. Such factors, more or less in the order of their importance, would include:

1. Effect of timing pesticide applications
   A. With respect to development of edible plant parts
   B. Exposure of edible parts
   C. Days before harvest
2. Rate applied
3. Rate of loss
   A. Decomposition or degradation
      (1) Normal range and average
      (2) Effect of temperature
      (3) Moisture, sunlight
   B. Rate of evaporation

C. Rate of erosion
   (1) Rainfall
   (2) Wind

4. Dilution due to growth of plant
5. Absorption by plant parts or substances
6. Availability and use of practical residue-removal methods
7. Miscellaneous
   A. The effect of methods of formulation on any or all of the above factors.
   B. Number of applications may be a factor, but in most cases the date of the last treatment will be more important.



BASIC CONSIDERATIONS IN THE DEVELOPMENT AND MARKETING OF A NEW AGRICULTURAL PESTICIDE INTENDED FOR USE IN CONNECTION WITH FOOD PRODUCTION

The introduction of new pesticides for use on food crops and livestock is a matter of public concern. So many new chemicals have been discovered for controlling insects, plant disease agents, and weeds that farm operations are being drastically changed. All of the available evidence indicates that even more new chemicals can be expected during the next few years. Sound policies must be observed in their evaluation and introduction.

These new materials would not be introduced and could not survive if they did not serve a useful purpose and improve our food supply. Since they are needed, every effort should be made to encourage the research necessary for their devlopment and to assure their use as soon as they can be introduced without jeopardizing the food supply or the health of the consumer.

Because of the wide variability in the chemical and physical properties of these materials, the crops on which they are to be used, and their response to climatic conditions, each chemical presents problems peculiar to itself. However, studies made by the Food Protection Committee during the past year have revealed many basic considerations in which there is general agreement among government agencies, industrial concerns, agricultural scientists, and food technologists regarding the evaluation and testing of pesticides prior to commercial use. Some of these basic principles are summarized in this report.

A primary objective of American agriculture is to provide an abundant supply of nutritious, wholesome food. Through war and

peace this objective has been attained, with reasonable surplus to help less fortunate neighbors of the world through their major food crises. The bounty of our farms has become so legendary that many people have come to believe that we have an inexhaustible supply of foodstuffs. Unfortunately, this is not true.

The food requirements of the past thirty-five years have been met at the price of drastically lowered soil fertility and the ruination of about three-quarters of a million acres by soil erosion. Meanwhile our population has been increasing at the rate of about 6,000 persons a day. The increase during the period 1940-1950 was the largest of any decade in our history. The food requirement of the United States is estimated at about 18 per cent more for 1960 than it is today. It is possible that American agriculture could, without the use of pesticides, produce sufficient food to provide a minimum calorie diet for our population. But without pesticides, most fruits and vegetables cannot be produced in the variety and quantity required to supply an adequate diet of protective foods.

In view of these facts, efforts to improve the efficiency of food production must include the suppression of insects and plant diseases that now destroy 15-20 per cent of our crops. We need better chemicals to reduce such depredations, particularly in those cases where pests are becoming more resistant to the commonly used pesticides. For example, there is ample evidence that the codling moth on apples became so resistant to lead arsenate that extra heavy spray applications had to be used. Also, some insects have shown increased resistance to DDT within the comparatively few years that it has been used extensively.

There are two national laws designed to protect our food supply against loss in productivity and against becoming a hazard to the health of the consumer. The Federal Food, Drug and Cosmetic Act of 1938 specifies that chemicals may be added to foodstuffs only if they are non-poisonous or necessary for food production. If

toxic materials are indispensable they are to be permitted only at such concentrations as will present no hazard to the consumer. The Federal Insecticide, Fungicide and Rodenticide Act of 1947 provides that no material shall be registered for sale in interstate commerce until complete specifications have been filed and data presented to establish its usefulness for the purposes claimed and its safety when used as prescribed.

The government regulatory agencies do not certify the usefulness of a material or provide data to the public on the comparative performance of different substances beyond assuring themselves that they will be reasonably effective and safe to use. The forces of competitive enterprise regulate prices, extent of use, and general acceptability.

The manufacturer of a new chemical and the appropriate government regulatory agencies must assume certain responsibilities to the public when pesticides are placed in commercial use. Government must protect the public from fraud and safeguard public health, and it has a moral and legal responsibility to establish and enforce tolerances for materials on food crops which may present a hazard to the public. In addition to his responsibility with respect to public health, the manufacturer must assume the usual responsibility for performance of the product as claimed, and within this responsibility, he should be granted a reasonable degree of freedom to incur well calculated risks pertaining to crop damage and performance of the material as a pesticide.

Before any new pesticide is marketed, its performance and safety, when used in the proposed manner for the specified purpose, should be clearly established. 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 performance and relative safety. Data on important points should be of such nature and magnitude as to be reasonably conclusive and/or to permit statistical evaluation.

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 necessitate or warrant conformance to all categories listed and, therefore, requirements should be properly restricted in accordance with proposed end uses.

PROPOSED EVALUATION PROCEDURES

I. *Chemical and Physical Data*

The following information should be as complete as possible; however, it is recognized that in some cases it may not be feasible to supply all of the information requested. The data supplied should be for the commercial or chemically pure grade of the pesticide, and not for formulations thereof.

A. Chemical name and structural formula. (Include here trade names, abbreviations, code numbers, and any other designations used to identify the compound in the literature and elsewhere.)

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. (Include here 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, such as density or specific gravity, refractive index, spectra, etc. These secondary characteristics are especially necessary if the pesticide is not a pure chemical compound.

H. Stability and reactivity. (Include here information on speed 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.)

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 or in the soil.

II. *Biological or Use Data*

A. Necessity or Justification for Use

To cover the wide variation in conditions that prevail, a general overall set of criteria, as outlined in the categories listed below, is necessary to establish pesticidal effectiveness, which in most cases will constitute the justification for use. However, the emphasis to be placed upon any single criterion will depend upon the nature of the pesticide under consideration.

1. *Criteria:* Pesticidal effectiveness should be established in terms of percentage reduction 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 other economic gain or practical benefit would include: economy or ease of production, harvest, or storage of the crop; flexibility as regards 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.

Supplemental information accompanying experimental data should provide a comprehensive description of the material and its use and should include the following information 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 of minor adjuvant ingredients should not be considered essential.
(b) Rate of dilution for use, if any.
(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 neither food plants nor animals are being treated (barns, ornamental, 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.

2. *Experimental Data*

(a) Laboratory Tests. The results of laboratory tests for the evaluation 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 action or use will largely determine the suitability of such data as a principal basis for evaluations.

(b) Small Plot Tests. The amount of data obtained in small plot tests should be adequate to demonstrate proper performance under natural conditions. The proposed end 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 covering 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.

(c) Large Scale Field Tests. These should be made on farms using commercial type of 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 regular use. However, the information desired here may be considered as partly interchangeable with that obtained under the heading "Small Plot Tests". Laboratory and small scale field tests may be used interchangeably with or as a supplement to field test data, depending upon circumstances and conditions.

B. Safety for Plants and Animals

1. *Plants.* Data should be collected as to plant injury, if any, in connection with the performance tests. Careful notation should be made of the type of injury, if any, such as 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.* Similar data should be obtained as to irritability, etc. where the pesticide is proposed for use on animals.

C. Compatibility

Compatibility data should be supplied where the product is suggested by the manufacturer for use with another pesticide or additive. Data on compatibility with other materials are desirable but should not be considered necessary unless such materials would obviously be used in the same spray schedule in accordance with recognized practices.

D. Reduction in Quality of Food, Including Adverse Appearance, Flavor, or Taste

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

E. Accumulation in Soils (Soil Residues)

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

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 purpose, 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.

Where pesticide residues may be anticipated on or in the food product, forage, or animal product, at the time of

harvest or slaughter, data establishing the residue remaining after effective dosages under optimum conditions for retention over the maximum time period of application should be considered essential. These data, which may be obtained from representative material employed in 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 would be required for pesticides which have no toxicity to warm-blooded animals at recommended dosages, are highly volatile or otherwise non-residual, or are decomposed to non-toxic components before harvest.

If a potential hazard is disclosed by the preliminary data on the amount of residue or toxicity potential 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.

Bioassay methods of demonstrated reliability may be used in lieu of chemical residue determinations where satisfactory chemical methods have not been developed.

If excessive residues are detected, methods for their removal should be developed.

G. Operational Hazards

Where necessary, proper precautionary procedures relative to handling and use should be developed.

III. *Toxicological Data*

A. Safety or Hazards of Use

Many of the pesticides, particularly insecticides, are known to be toxic. Data are needed to provide for: first, a clear delineation of the toxicity of the compound, as regards both qualitative and quantitative factors; 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.

It should be noted that no available technic is capable of giving absolute assurance that a food or water containing a pesticide is completely safe to all humans under all conditions. Thus it is possible to determine beyond reasonable doubt the harmlessness of a given chemical additive in food or water, but to prove its absolute safety is impossible.

B. Determination of Toxicity

Toxicity must be established in terms of generally accepted indices of injury, such as structural, biochemical, or physiological changes in specific organs or body systems.

No single rigid program can be laid down which will apply in relation to every new pesticide in all its possible applications. Data developed in one phase of an investigation may serve to show either that experiments included in original plans are superfluous or, on the other hand, that original plans must be expanded to elucidate more fully some critical findings.

For determining the advisability of program curtailment or expansion at any given point, on the basis of toxicological findings, only one rule can be laid down: such decisions must be made on the basis of the facts in the immediate situation by toxicologists qualified by scientific training and experience to assess such situations. It is obvious that use data or other non-toxicological factors also operate in instances to influence the scope of the toxicological program. Evidence of a broad field of usefulness against many crop pests might dictate a more extensive program than originally contemplated, while failure of the compound in small plot tests would almost certainly lead to its discard.

With these factors in mind, the following tests should be included in a tentative program which could be reasonably expected to yield the toxicological data needed to assess hazard.

1. *Acute Toxicity.* As a minimal program the LD_{50} should be determined in at least two species and in one of them by at least two routes of administration, the oral and an appropriate parenteral route. Sufficient animals must be used to permit statistical evaluation of the reliability of the LD_{50} values determined. The rat and some other rodents are usually satisfactory for this purpose. In addition, the acute oral LD_{50} in rats should be determined for the finished commercial formulation, to ascertain the influence of other ingredients on the acute toxicity of the active ingredient under study.

   Sufficient acute toxicity data should be obtained in dogs to permit a reasonably accurate estimate of the lethal dose in that species.

   For the benefit and protection of those who must apply the material in crop testing and thereafter, 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, symptoms, and clinical course of poisoning, and if possible the mode of death, should be described.

2. *Subacute Toxicity.* (Generally regarded as any toxicity test of a duration shorter than one year.)

   (a) *Oral.* A 90-day feeding test in rats may be regarded as economical in that it yields many needed data for a relatively modest expenditure in time and funds. Ten

animals of each sex at each of several feeding levels should yield information which may determine at this point whether the proposed use is too hazardous to warrant further toxicological study. The information obtained may also serve as a guide in selecting feeding levels for the chronic study.

The data sought may include, at each of the several feeding levels, the effects in relation to growth, mortality, blood changes, and organs as measured by both weight and histopathologic findings, and such alterations in functions and behavior as may be apparent from gross observation. Also the chemical analysis of tissues may yield valuable preliminary information with respect to storage.

(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 is applied daily to the clipped skin, care being exercised to avoid ingestion by licking. The indices of injury enumerated in the preceding paragraph also apply here.

3. *Chronic Oral Toxicity.* (Now generally regarded as lifetime or two-year feeding in the rat and one year or longer in the dog or monkey.) Such 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 with tests less stringent than lifetime feeding in a short-lived animal such as 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 stringent than necessary, but the presently available backlog of data has not furnished a more rational alternative.

(a) *Rats.* Usually the material under test is fed in the diet to weanling rats at several levels, including a control

diet containing none, with ten or more rats of each sex at each level. The levels to be fed should be chosen on the basis of the data obtained in the subacute feeding tests, an effort being made to select levels which will include one which will produce no effect, one definite damage, and one or more intermediate in effect.

When time is a pressing factor, the subacute rat feeding test may be so set up that a sufficient number of rats at each dietary level can be continued for the two-year period if the 90-day data indicate the desirability of so doing.

Data collected in the two-year tests may include those on growth, reproduction, mortality, organ weights, histopathologic and hematologic findings, blood and urine chemistry, tissue storage, excretion, the occurrence of blood dyscrasias or cancer, such changes in behavior and function as may be determined by gross observation, and such other data as may be dictated by judgment in special circumstances .

(b) *Dogs or Monkeys.* Three or more adult animals are usually fed the material under test at three or more dietary levels for one year or longer. Similar data are sought as in the chronic feeding tests with rats. The dog or monkey tests are generally started after the rat tests have been in progress long enough to provide data to aid in selecting the feeding levels likely to be most informative.

(c) Where human exposure has occurred, all appropriate tests should be employed to determine whether there have been any physiological or other effects.

4. *Pharmacodynamic and Biochemical Investigations.*

(a) *Pharmacodynamic.* The pharmacodynamic tests will vary in scope, the aim being to describe the effects brought about in functional systems and the mode of action of the compound. There exists no succinct way of describing the possible 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 therapeutic treatment of accidental poisoning if technically possible.

(b) *Biochemical.* These investigations should be designed to discover the extent of absorption, detoxication, accumulation, storage, and excretion. Here again the investigation's scope will vary from compound to compound and with the intricacy of the processes, which should be elucidated. The minimal program should seek to describe the routes of absorption and excretion, the extent and site of storage, if any, the rate of release from depots, and the functional implications thereof.

5. *Special Considerations.* In the interpretation of the toxicologic data, emphasis should be given qualitative factors, including among others:

(a) The uniformity of response within and among species.
(b) The occurrence of unusually alarming reactions, as carcinogenesis or blood dyscrasias.
(c) The occurrence of sensitivity, tolerance, or idiosyncrasy in response to exposure to the compound.

C. Determination of Hazard. Once the toxicologic data have been assessed and the toxicity of the compound adequately described, there remains the task of estimating hazard by balanc-

ing toxicity against possible intake. In this a number of considerations become pertinent, including:

(a) The nature and degree of adverse effect which the pesticide may produce and the class of persons which may be affected by it.
(b) The proportion of the usual diet which is composed of foods in which the pesticide may appear.
(c) The amount of the residue that will remain in foods when the pesticide is used in accordance with accepted practices.
(d) The likelihood of gross misuse of the pesticide that might lead to excessive residues.
(e) Whether the pesticide is to reach the consumer by direct additions to food or indirectly through animals which have consumed the pesticide.
(f) The possibilities of alteration of the pesticide after its addition to foodstuffs or consumption by animals.
(g) The extent of the presence of chemically or pharmacologically similar substances already in the usual diet.
(h) The ease with which persons may avoid foods containing the pesticide.

IV. *Coordination of the Development of the Chemical, Biological, and Toxicologic Data.*

The foregoing sections make apparent the magnitude and complicated nature of the broad research program required for the development of a new pesticide, involving the efforts of several different groups of investigators. In such a venture, integration of effort is a necessity if excessive costs in time and funds as well as undesirable delays in the development and marketing of needed pesticidal compounds are to be avoided.

For example, analytical methods should be developed early in order that residue levels on edible crops shall be defined and the

data made available to assist others in planning intake levels for chronic toxicity studies. Analytical methods should be further refined for use in biological fluids before pharmacological and biochemical studies are undertaken.

Information on acute and subacute toxicity adequate to define operational hazards should be in hand before agricultural workers are exposed extensively in field tests.

Complete knowledge of many factors pertaining to pesticide usage, performance, and ultimate safety can be developed only through actual use in large scale performance tests. Hence, any system proposed for regulating the distribution of new materials should provide for their orderly release with recognized steps between strictly controlled small plot experiments and full scale commercial operations. Only a portion of the desired data can be obtained through observations on usage on non-food crops. Therefore, progress would be greatly enhanced by large scale experimental or otherwise provisional use of a promising material on a nominal percentage of a given crop as soon as residue and subacute or preliminary chronic toxicity data establish its safety beyond a reasonable doubt. Since chronic toxicity largely pertains to a continuous intake of marginal quantities of a chemical over long periods of time, the possible temporary occurrence of such a residue on a nominal percentage of a crop would create no undue hazard. If, however, residues greatly in excess of the anticipated or safe level are encountered in large scale or semi-commercial treatments, the product in question should be withheld from the market and not used for human or animal food. The proposed procedure would permit the earlier safe development of a pesticide because voluminous data not otherwise obtainable could then be accumulated during the period in which final detailed toxicological studies are being conducted to develop more precise chronic toxicity data on which ultimate safe residue levels for the crop as a whole could be based.

The attached chart represents an attempt to portray graphically a workable plan of integration of effort among the chemical, agricultural, and toxicological teams working on a given compound. Special circumstances often dictate changes in such a general scheme and it may be modified to meet problems unique to individual investigation.