HANDBOOK of TOXICOLOGY

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HANDBOOK
of
TOXICOLOGY

Volume III: Insecticides

A Compendium

By

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Prepared under the Direction of the Committee
on the Handbook of Biological Data

DIVISION OF BIOLOGY AND AGRICULTURE
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INTRODUCTION

In sponsoring the Handbook of Toxicology, the United States Air Force, through the Wright Air Development Center, foresaw from the outset a volume, or at least a section, on insecticides. The present book, dealing with the toxicity of insecticides and such ancillary substances as acaricides (miticides) insecticide synergists, repellents, etc., is the outcome. The goal of this book has been to bring together as completely as possible and in convenient form data—preferably quantitative, tabular, and comparative—derived from valid tests by explicit methods, on the subject of insecticide toxicity.

Implicit in the subject of insecticide toxicity is the topic of hazard to man, to domestic animals and plants, and to plants and animals in nature. Hazard may be particular, unique to certain circumstances or in absence of certain reasonably attainable precautions, or it may be universal and ever-attendant upon the simple existence of a toxic agent. Hazard may accompany the synthesis or manufacture, the compounding or formulation, or the general or special use of an insecticidal substance. During synthesis or manufacture, hazard may be far more acute than in final use, since the primary materials or processes may be far more toxic than the end product, or be far more difficult to control in their harmful potential. The inverse, of course, may just as easily be the case. Hazard and toxicity, then, must be carefully differentiated but the degree of hazard cannot fully be measured without exact knowledge of the toxicity. Hazard and risk, biologically speaking, are inherent in insecticides as in any other biologically potent agent.

By definition, an insecticide is a substance, a mixture of substances, or an agent used to kill and thus to control insects and related arthropods. In actual use, insecticides are intended to apply only to species harmful or annoying to man and his chattels or property. Unfortunately, in most cases the insecticide must be applied to the undesirable insect in a context of other living organisms, plant or animal, which may be also subject to the life-harming powers of the insecticide. The goal, plainly, is to have insecticides which are highly specific in their action, acutely effective in harmful properties for the undesirable forms of life, while being innocuous or only slightly, and so controllably, harmful to other living forms. With chemical agents as insecticides it is not always easy to attain such specificity. What may be lethally harmful to insects by in any way altering or disturbing their normal vital processes may entail harm for other living organisms. It is necessary, however, to guard against an automatic assumption that high hazard exists in the use of any and every insecticidal agent. Hydrogen cyanide is a gas acutely toxic for virtually all animal organisms, and nicotine is an alkaloid which, unit for unit, is almost incomparably poisonous for higher animals; yet both these substances have long been used for insect control in a completely routine manner, with proper precaution, by persons not chemists, pharmacologists, toxicologists or zoologists, and without harm to themselves. The important thing is to know and understand where and under what conditions even a highly poisonous substance may be employed with a minimum of hazard. For long-familiar insecticides the conditions of use, of precaution, and of control are, on the whole, well-known. But nowadays new insecticides are multiplying upon the scene in many guises, under many names, in many formulations. Until about twenty years ago, new insecticides made their appearance in a thin trickle. With the arrival of DDT, the trickle became a freshet, and the freshet now attains the dimensions of a flood. But advances in knowledge of the special nature of insects and their close relatives have also multiplied—many of these advances resulting from a search for methods of control and the test of putative or potential insecticides. By knowing more fully the special nature of insects and those weaknesses peculiar to them, advantage may be taken of such special attributes to attack the insect while leaving safe other living organisms.

By concentrating primarily on the toxic properties of insecticides, the present work might expect to achieve usefulness as a general guide to the degree of hazard, viewed broadly, that attends the use, under reasonably well-defined conditions, of any insecticide presently in general use or rapidly achieving general use. The comments made under Acknowledgments have already indicated that any value this book may have rests solidly on the original scientific data of a host of workers. Only by considering and comparing many data, and allowing for various methods used under specified conditions, is it possible to consider the range of action of a particular agency. This work considers data drawn from controlled laboratory experiment under defined conditions as well as data, and certain "value" conclusions, derived from field experiences whose conditions are far more difficult to define and control. A recognition both of the relatedness and the essential differences that distinguish the classes of data gathered by these two general methods has led to their being quite strictly set apart from each other in this book. Although this will help to provide understanding, forewarning, and control of hazards associated with insecticidal use of chemical agents, such putative utility must be a by-product—a consequence of knowledge presented disinterestedly and without bias. Comprehension of this ideal does honor to the United States Air Force which, in the immensity of its activities, has recognized the primacy of knowledge and sought to promote it in so many fields.

Aside from usefulness in the assessment and control of hazard, other useful results may arise from the comparative treatment of the data as these concern groups or families of substances related chemically and structurally, or related by an essential similarity in mode of detailed action. Toxic action is physiological action, biochemical action. The toxic action as such may be the one on which we focus attention, but that toxic action may shed valuable light on the general physiology of a biological group of such high importance and interest as the insects. Thus, as Sir Francis Bacon long ago insisted when induction as a method, if not as a practice, was young—data brought together in an orderly and comparative way may in the hands of the thoughtful and imaginative readily suggest fertile associations and fruitful generalizations.

A given insecticide is not equally effective or similar in its action upon all insects. This very fact may lead to deeper knowledge about both the insects and the nature of the insecticide. The quest for new, useful agents of chemical control of insects is nowadays far from being wholly and blindly empirical, as once it was. Newer knowledge of insect physiology—and what may rightly be termed insect pharmacology and pharmacodynamics—has revealed that certain general types of chemical structure act on insects. Such information makes possible a more clearly-directed search for agents with sharper and more specific insecticidal use. Indeed, it may be said that to a fair extent insecticides may now, in a chemical sense, be designed deliberately. In that activity this book may, in a very practical manner, be helpful.

From the outset it was deemed more fruitful to deal generally with the toxicity of insecticides for all living organisms, whether mammals or other vertebrates, insects, other invertebrates, or plants. Also it was apparent that a work on insecticide toxicity would be gravely incomplete and grossly limited if it ignored a proper setting forth of what is known or reasonably conjectured about the modes of pharmacodynamic action (and so toxic action) of the compounds dealt with. This imposed another dimension on the work and required an orderly comparative treatment of physiological, biochemical, pharmacological and pharmacodynamic data, as well as of the pertinent aspects of the physical and chemical properties of the compounds.

Emphasis, or apparent emphasis, upon the toxicity of insecticides entails certain touchy consequences. The risks and hazards of insecticide use have been both grossly exaggerated and grossly underestimated and they will continue to be until sufficient data are properly available to give unbiased persons a basis for valid judgment. One extreme view finds an inherent harmfulness in the use of any chemical agent in agriculture or forestry and holds that a healthy plant (brought, of course, to maximum vigor by the use of organic fertilizers only!) tolerates and overcomes any and all insect attack—a view often coupled with the conviction that insecticides are an unmitigated threat to the balance of nature. Another extreme view results in an indiscriminate, overenthusiastic use of insecticides without regard for real problems of toxic hazard in their many aspects. Attainment of some golden mean is the hope and the object of this book. Certain dangers to the balance of nature may always be a possible consequence of large-scale human activities. Yet, it may be reasonably expected that man, having an ingenuity sufficient to upset the balance of anything so majestic as nature, will find in himself an ingenuity equal to redressing the balance. It is quite true, for instance, that large-scale, intense use of certain chlorinated hydrocarbon insecticides to control leaf-eating insects may bring on great upsurges in the numbers of sucking arthropods, such as aphids and mites, because of a coincident decimation of their natural enemies. Such a situation calls for more knowledgeable use of combinations of agents having a range of action sufficient for the simultaneous control of the several harmful forms. A deeper understanding of the subtleties of the natural balance is needed and a greater foresight in testing and evaluating putative insecticides under many circumstances.

Such dangers do not diminish the value of insecticides wisely and skillfully used. Even the achievement of complete specificity in insecticides would not entirely remove all hazards, and certainly not the hazard to the balance of nature. Even those insect species supremely noxious to man have their place in that balance. The imperative laid upon man is that of judgment founded on wide knowledge in weighing one danger, one hazard, against others and mastering them all. The balance of nature on the North American continent was no doubt in quite suitable adjustment before the arrival of the Japanese beetle. A specific, or a method, that would once and for all remove this undesirable immigrant from the North American scene would not, wisely applied, harm nature by one bit.

This book has its severe limitations—limitations self-imposed in the original conception of the work. Some of these are later described so as to indicate to what extent the work proposes to have valid scope and wherein it does not propose to have competence.

Thorny problems attended the conception and the growth of the work. It was imperative to present the facts in such a way that the source of any particular one might be quickly apparent to the reader, and to accomplish this without loading the text with an excessive freight either of direct bibliographical citation or of numbers referring to a cumulative bibliography. The bibliographic problem was a major one because of wide variations of data referring to the same or similar situations. Large variations in results offered by several workers do not imply that all are wrong or that one alone is right. Method of test and experiment, nuances which attend a given occasion, the nature of the test insects or animals themselves—a multitude of factors too numerous to pursue—are at play as sources of variation. These the reader must be able to trace and evaluate from the sources. In this field as in others, the best and most useful methods have not yet necessarily come to light or moved to the fore. At this stage it appears that data attained by many methods properly and honestly applied must be presented. Indeed, the variety in the data itself points to the inherent complexity of problems and to the need for deeper knowledge and new approaches.

How to set forth information so various and from so many sources was answered (wisely, it is hoped) by combining, as the nature of the data demands, tabular, semi-tabular and frankly textual (but outline) methods. Running text was the resort in fields and topics which resist tabulation or where tabulation might mislead by producing a false impression of finality and certitude. This last is a risk ever-present in tabulating and presenting together data from many disparate sources without adding details or indications about method or the conditions of experiment or observation. As opposed to tabulations with an elaborate and confusing apparatus of footnotes, a simple outline text was deemed more useful for much material. By setting text statements in outline with designation by numbers and letters, attribution of facts to a marginally indicated source became possible.

The task undertaken loomed appallingly great when it was soon evident that data contributed *ad hoc* by their originators would not be forthcoming with sufficient completeness and balanced emphasis or, above all, within a practical period of time. To bring off the project at all, the author had to gather the data directly and all but wholly from published sources. The gathering of materials, their organization, and the composition of the manuscript took from September 1955 to March 1957. Contemporaneous data were added steadily during the months of preparation. Pertinent additions were made to the text as completed in March 1957 from publications appearing through the whole of 1957. Addition of such supplemental recent data ended in February 1958. These facts are recorded to allow the reader to judge the contemporaneity of the book's content.

A word of caution is needed. The Table of Contents shows many names of substances quite widely familiar as designations for insecticides in the open market or frequently appearing among the active ingredients listed for insecticides sold under various proprietary names. At almost any point a glance at the text will show various insecticidal substances comparatively treated in the tables in terms of toxicity. Comparative rankings founded on degree of toxicity measured in various ways under controlled experimental conditions have, to be sure, their proper worth in evaluating insecticidal potential. They have, however, little to do with the relative merit of this product or that as ingredients of field, garden, or household insecticides under conditions of diverse general use. Such ranking must not in any way be taken to mean that this book, the author, the sponsors, or the publishers individually or collectively recommend one substance over another or one insecticide in preference to another in any situation. Not even in those instances where it may appear that in field experiences substance "A", for example, was ineffective or proved less effective than substance "B" in degree of mortality yielded or extent of control given for a particular insect species does this imply a general value judgment of the relative worth of substances "A" and "B" under wide and diverse conditions of use. In the laboratory a compound may show great range of useful activity against the relatively small number of test insects usually employed as laboratory subjects. If it is as an insecticide of wide "spectrum" that the compound is intended it may well be far less promising against the multitude of species of undesirable insects to be coped with in nature. A compound which in a specific kind of laboratory test proves to be the most toxic of a group or series of compounds may under field conditions (or even in another type of controlled test) be precisely the least effective because of other physical or chemical properties.

As an example, nicotine sulfate under some conditions and acting upon certain insect species is a superb and even ideal contact insecticide. Unit for unit, nicotine sulfate may be, judged in tests based on LD_{50} or other criteria, greatly more toxic than a substance designated as "X" when both are tested by intraparenteral injection into individuals of a particular insect species. Let us assume, however, that "X" is designed for use as a residual insecticide of long-lasting action—a role in which it has proved valuable. For all its effectiveness as a contact insecticide nicotine sulfate as a residual insecticide is all but useless because of its notable evanescence. Under specific conditions the high contact toxicity combined with evanescence may be just the combination of properties most to be desired. Under other conditions the property of evanescence may entirely cancel the advantage of high toxicity. Toxicity *per se* is but one of the attributes called for in an effective insecticide and need not be, categorically, the most determinant of effectiveness. Actually, under some conditions, extreme toxicity may prove a stumbling block to practical use of a substance as either a general or specific insecticide. All this is by way of saying that the data brought together in this book are expected to have value when judiciously and properly interpreted or used in the context for which they were originally, and in the present publication continue to be, intended.

It is not proposed as part of the scope of this book, to give an orderly treatment, however abbreviated, of the history of insecticides or of man's essays to fend off the depredations of insects. It may not be amiss, nevertheless, to remark here that man from the start suffered in his body and in his goods the damage and loss pressed on him by a host of insect species. Man's attainment to the rank of husbandman and cultivator certainly posed for him in a more acute form the endless contest between himself and these insidious and extraordinary adversaries. Just as surely he must very early have noted the beneficence and usefulness of many insects, notably the silkworm and the bee, and been excited by the vivid beauty of others. A testimony to the latter is the jewelry of irridescent beetle wing cases worn by the Papuans. Attempts to evade the despoliation of his crops, gardens, and animals by insects, doubtless led man from Neolithic times, if not earlier, to meet his competitors the insects by many means, some perhaps crudely chemical. In the folklore of peoples there is mention, and in the folkways there is use on a local scale, of plants and plant products which have or are reputed to have insecticidal worth. One need only recall that some peoples accounted primitive have shown high skill and cleverness in the use of plant products as fishing and hunting poisons. The use of rotenone-bearing plants as fish poisons or stupefiants is a case in point. The fly-killing properties of some daisy-like flowers containing pyrethrins, where these are native, have evidently been noted from immemorial times. Homer has sung of the "divine and purifying powers" of sulfur burned in ritual purification.

With what success man fought his insect foes there is but little record until quite recent times. But, whatever man's success may have been on a small scale in earlier, or on a more far-reaching scale in later times, there is to this day no triumph of conquest-by-extinction of a single noxious species. However, there have recently been great triumphs in chemical insect control on a regional scale, even to the point of elimination of some species from wide regions, but a permanent end to the struggle on any front is yet far to seek.

Weapons of great subtlety are being devised, some of them exceedingly ingenious. An interesting example is the use of high-energy, short-wave rays, (such as those from radioactive cobalt) to irradiate male warble flies to the point of extinction or suppression of normal spermatogenesis and the subsequent release of these treated males into the environment. Such males suffer no obvious disability other than the one mentioned nor are they at a disadvantage behaviorally in the external aspects of sexual competition. However, their insemination of, or copulation with, females—an act taking place but once in the life-cycle of the latter—leads to a life-long laying of sterile eggs. But the wheelhorses of insect control will probably continue to be chemical agents, increased in number, reduced in price, cunningly designed and refined for ever enhanced and more specific action. Occasions may well arise on which we may, after a period of desuetude, resume the use of some of the older agents. Calcium and lead arsenates—insecticides of ancient lineage—were still sold ten years ago to the extent of fifty-five million (55,000,000) and ninety million (90,000,000) pounds respectively. Sulfur, for fungicidal and insecticidal purposes, was used in the amount of two hundred million (200,000,000) pounds. In the same year the modern insecticide DDT was used in the amount of forty million (40,000,000) pounds.

The use of arsenic compounds as insecticides is commended in written accounts dating to the last quarter of the 17th century and their practical and effective use certainly antedated that period. The fungicidal effects of copper compounds on diseases of the vine in European vineyards was recognized in late Renaissance times. The insecticidal and fungicidal powers of copper and arsenic found employment as Paris green in the last quarter of the 19th century. From such sources stemmed a considerable arsenal of mineral insecticides many of high usefulness to the present time. Recognition of the insecticidal value of some plants, notably derris, appears to have originated in China. The Romans appear to have used Veratrum insecticidally and rodenticidally. No one knows how or where the numerous species of plants showing insecticidal virtues may first have been used. Kerosene emulsions to control several sucking insect pests came into use in 1877. A quite respectable group of synthetic organic insecticides was in hand beginning early in the first third of the present century, among them several fumigant agents such as methyl bromide, carbon disulfide and para-dichloro benzene. Thiocyanates and thiocyanoacetates were added to the armamentarium shortly after, as well as the highly potent and effective nitrophenol family of compounds. And, as noted before, since the advent of DDT as an insecticide in Switzerland in 1939 the flood-gates have been opened and synthetic organics have come to dominate the scene.

In arriving at the insecticides presently in vogue thousands of compounds from the chemical stockroom have been tested as well as hundreds of others synthesized *ad hoc* or available as byproducts of other investigations. Seeking substances to control and repel insects and other arthropods of medical interest led to the systematic testing of some eleven thousand (11,000) compounds by the Orlando, Florida laboratories of the United States Department of Agriculture alone. And so the story and the search go on.

The extent of the need for chemical control of insects, and indeed, for any other kinds of practical or available control, may be measured by the fact that of some eighty thousand (80,000) species of insects in North America, ten thousand (10,000) are noxious species of more than casual consequence. Their depredations are vast, estimated for the United States alone to cost some two billions (2,000,000,000) of dollars and to entail a loss of some ten per cent (10%) of the country's agricultural crop.

The Table of Contents of this book will be found to list one hundred and eighty-eight (188) sections. Of these one hundred and sixty-four (164) concern individual, specific insecticidal substances or ancillary agents. Twenty four sections—some quite lengthy, others short—deal with general topics or treat collectively certain properties and aspects of well-defined families of related compounds which show broad similarities of chemical structure and mode of physiological and pharmacodynamical action. The reader will certainly ask how and why the comparative handful of 164 insecticides dealt with in this book was selected from the many compounds having some insecticidal virtues and from the great number of compounds systematically tested. The criterion has been that a substance, on the basis of tests, must be an effective insecticidal agent either in general use or in economically significant specific use, or must have so qualified in the immediate past or give evidence of being about to attain such usefulness.

Some general description of the form chosen for the presentation of the subject matter will provide guidance in the use of the book and an idea of its scope and its limitations and thus of its competence and validity. First, it will be seen that each compound or insecticide has been dealt with individually, as an entity, with all pertinent material relating to the compound gathered under the heading--which is the compound's name. Since many compounds are similar in many aspects of their chemistry and action, this has led to rather frequent repetitions and even to multiple appearance under several compounds of the same comparative tabulation, but only slightly rearranged in each case to bring to the top the name of the compound specifically the subject of that section. This has come about, and is believed justified, because it was considered that a handbook should present succinctly in one comprehensive section or chapter everything pertinent to one compound or insecticide—without the annoying necessity of multiple cross references and endless leafing of pages in widely different parts of the book. A certain amount of repetition was considered a small price to pay for having the data coherently grouped in each separate section. Where common properties and modes of action, etc., are so similar as to have led to voluminous repetition of much the same set of facts, a general section was added for that particular natural group of compounds. Cases in point are the extensive general treatments of Organic Phosphates, Dinitrophenols, Fumigants, etc., in addition to the specific treatments of the individual members of each of these groups.

For simplicity's sake, individual sections of the book (those dealing with particular specific compounds), as well as the general sections, are presented in alphabetical order. Compounds are listed by their most common names, this being true even if such designations are trade names or names made up *ad hoc*, when these have reached currency of use. In the absence of such current common names, strict chemical designations are used. Also, each section at the very beginning gives the more usual synonyms by which a substance may be designated.

In the index of chemical names, where all compounds mentioned in section headings or text are given, all available designations for any compound are set down alphabetically, with appropriate cross-references. Thus, any one consulting the index for synonyms for Acrylonitrile, the first section heading of the book, will find: cyanoethylene, propenenitrile, or vinyl cyanide. Aldrin will be found under that heading but in the index also as 1, 2, 3, 4, 10, 10-hexachloro-1, 4, 4a, 5, 8, 8a-hexahydro-1, 4-endo-, exo-5, 8-dimethanonaphthalene, HHDN, Compound 118 or "Octalene". Allethrin may be found as such simply by looking for it alphabetically under the section headings but also in the index of compounds as dl-2-allyl-3-methyl-cyclopent-2-en-4-ol-1-onyl dl-cis-trans-chrysanthemate, dl-allylrethronyl dl-cis-trans-chrysanthemate or dl-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one ester of cis-trans-dl-chrysanthemum monocarboxylic acid. And so forth.

An alphabetical ordering of subjects also has certain inherent disadvantages. Chief among them is that families of related compounds whose members might otherwise be grouped under generic designations are sundered and scattered. This disability precludes also the association of all fumigant insecticides together, all systemic insecticides, all substances of plant origin, etc.

There exist several general types or groups of insecticides based on some prime mode of action or route of entrance into the insect body. Thus, a contact insecticide acts or kills when it comes in actual touch with the surface or integument of the insect. Now, if such an insecticide kills by making contact with the outer surface it may just as well have an equal action when brought in contact with an internal surface, such as that of the intestinal or alimentary tract, upon being swallowed or that of the respiratory organs on entering these. A stomach insecticide exerts its principal action when it enters the alimentary canal of the insect with that insect's normal food or in some bait attractive to it. Again a stomach insecticide may have good toxic powers by the surface contact avenue, as is true, for example, of sodium fluoride, some arsenicals, fluosilicates, etc. A fumigant insecticide acts in the form of a vapor or gas and enters the insect body primarily via the respiratory organs. It is not at all unlikely, however, that a fumigant may also, in some cases at least, pass as a gas or vapor directly through the general integument just as solid or liquid contact toxicants do. Indeed, a particular insecticide may act by any or all the routes of entry and kill in all three modes.

The several general types of insecticides may be classed further into sub-types on the grounds of nuances of toxic action. DDT, for example, kills by contact and by stomach penetration. Additionally, DDT has long persistence on a treated surface and is a contact insecticide potent enough so that an insect standing on, or otherwise touching, a surface holding a deposit of DDT may pick up by way of its integument enough of the poison to kill it. Such residual action is clearly a nuance of contact action, although the deposit, persisting for days or weeks, might just as well be taken by mouth in the case, let us say, of a leaf-eating insect as to be taken through the integument of an insect resting on a DDT-coated leaf. By contact, nicotine sulfate exerts a most potent toxic action on soft-bodied insects but it is toxic, and intensely so, for all insects when ingested. Also, nicotine sulfate being volatile, it may have a short range fumigant action by vaporization from treated surfaces or be used intentionally as a fumigant by vaporizing it in a closed space such as a greenhouse.

A new and fascinating class of insecticides—the so-called systemic insecticides—acts by various ways. They may kill by direct contact, by residual action, and by direct fumigant action. But, more subtly still, they also enter the tissues and the sapstream of plants there to serve as stomach poisons to insects feeding on the plant's tissues or juices. By metabolic transformation in a treated plant, such systemic insecticides may yield compounds decidedly more toxic than the substance applied originally. Of course, the converse may also be true in the case of other "systemics". Furthermore, some "systemics", or their metabolites, may pass from the plant as vapors in the transpiration stream and poison, as volatile fumigants, susceptible insects present within the range of their action. Some few compounds, transmitted via the blood and tissues of treated test animals, have been shown to exercise systemic action upon insects or arachnids normally feeding upon such animals as biting or sucking parasites.

Although an insecticide may be poisonous to insects by various routes of entry, the toxicity is not necessarily of the same degree by the several routes; to be lethal, penetration by one route may require a higher dosage than by another. Thus, in toxicity tests it is necessary to state precisely by what avenue of entry a toxicant has been applied to a test organism. In every instance where it has been possible to make this most significant specification it has been given in this book.

An insecticide may show wide variation in toxicity and in the speed of its action depending on the manner of formulation. Thus, if a toxicant is applied in solution the solvent may exercise a powerful influence, or if it is applied as a solid mixed with or diluted by another solid, as in a dust formulation, the diluent may strongly modify the action. Further, an insecticide's toxicity may be enhanced or potentiated in many ways by auxiliary or adjuvant agents.

Rarely are insecticide compounds used in the pure or undiluted form, a usage which would in most cases be both wasteful and overly costly. The physical state of an insecticide—for example, a viscous liquid—may preclude its use in the undiluted state, even if there are no other impediments. Thus, insecticide chemicals are ordinarily formulated in a variety of ways. They may be dissolved and/or diluted in liquid solvents, mixed with solids as dust diluents, or treated in a manner to render insoluble and hydrophobic types wettable so that they may be prepared as solid suspensions or liquid emulsions suitable for spraying. Diverse materials may have been added in formulation to act as adjuvants, synergists, stabilizers, potentiators, "safeners", emulsifiers, surface-active or detergent agents, etc. Not only may such treatments make the insecticide more easily or effectively applicable by any one of many methods but they may influence or alter profoundly the toxicity of the insecticide component for insects or related arthropods as well as for animal organisms or plants. To be fairly and usefully presented, data on toxicity should include the nature of the formulation or the physical state of the insecticide in precise form. Especially is this meaningful in any exact consideration of phytotoxic properties since in many cases the insecticide proper may be quite harmless to a plant, whereas a solvent in which it is dissolved or diluted may be decidedly harmful.

Except for fumigants, which are usually gases or easily vaporizable liquids or solids, insecticides are most usually formulated or prepared for application in the following forms:

Solutions, Emulsions, Aerosols, Dusts, Wettable powders.

An insecticide solution is simply the insecticidal chemical dissolved in a liquid in which it is soluble. The solvent and the concentration of active ingredient(s) may be such that the solution can be used directly. Usually, however, insecticides sold in solution are concentrated and must be further diluted. The simplest case, of course, is that of an insecticide dissolved in water, but the majority are not soluble in water to any great degree. Such agents may be dissolved in other solvents, such as oils or organic solvents. In turn, such solutions may be suitable for direct use or may be further diluted. (Certain solution formulations are known as emulsifiable, emulsible or emulsion concentrates, a designation which is defined immediately below.) Since insecticides must often be applied to surfaces (including the insect surface) which are not readily wettable by water or aqueous solutions, surface active agents, detergents or spreaders such as soaps, sulfonated compounds, sulfated alcohols, dried blood plasma, etc., may be added to enhance spreading, wetting or adhesion.

An insecticide emulsion indicates a liquid insecticide which is insoluble in water but which may be brought by appropriate treatment into a state in which it is suspended in water in fine droplets. An insecticide, solid or liquid, also may be dissolved in a suitable solvent (such as one of the many organic solvents) which is itself insoluble in water but which can be emulsified in water as more or less stable suspensions of fine droplets. Such concentrated solutions of insecticides in an organic solvent are the emulsible, emulsifiable or emulsion concentrates mentioned parenthetically above. Such an insecticide in concentrated solution in the organic solvent is suspended in water in the droplets of the dispersed phase of the emulsion. Emulsification may be promoted and the emulsion stabilized by use of diverse materials, soaps among them. If the insecticide is directly emulsified in water, the application of this emulsion, after evaporation of the water, leaves a deposit of the insecticide upon the treated surface. In the case of the emulsifiable concentrates, if the organic solvent is non-volatile after the evaporation of the aqueous phase of the emulsion a deposit of insecticide is left in solution in the non-volatile solvent of the concentrate. If the solvent present in the emulsifiable concentrate is, however volatile, evaporation of both the aqueous phase and the organic solvent will leave a direct deposit of the insecticide upon the surface.

An aerosol represents fine particles suspended in air as fog or mist. The term, however, is commonly used to designate an insecticidal chemical dissolved in a liquefied gas which is kept liquid under pressure in an appropriate container which may be the "tin can" of the common "aerosol bomb" or a similar but slightly more substantial re-usable container. A common substance used to dissolve insecticides for aerosol use is the refrigerant gas dichlorodifluoromethane with a vapor pressure of about 75 lbs. per inch square at 20° C. However, aerosols, in the strict sense of a cloud or mist of fine particles, liquid or solid, suspended in air may be created by burning (the so-called insecticidal "smokes" or "pyrotechnic mixtures"), mechanical atomization, heat vaporization, etc.

An insecticidal dust may represent neither more nor less than a solid (i.e., non-liquid) insecticide applied to surfaces or distributed in the form of very find particles. Most frequently, though, what is meant is a melange of an insecticide or insecticides in a finely ground solid diluent which may be any one of the various clays, earths, diatomaceous earths, talcs, chalks, finely ground organic flours such as powdered nut shells, etc. Silica gel and alumina are examples of light or "low bulk density" dust diluents, while talcs, clays, and pyrophyllite exemplify heavy or "high bulk density" diluents. To prepare an insecticidal dust, an insecticidal substance may be directly mixed mechanically with the dust diluent or may be prepared in the form of a solution (as in an organic solvent) which is then introduced as the dust is ground or tumbled. Evaporation of the solvent then leaves the insecticide in fine particles distributed in the dust.

An insecticidal wettable powder represents a finely ground or fine particulate solid or mixture of solids, among which, of course, must be the insecticide itself, prepared or treated in such a way that it may be readily "wetted" or rather dispersed as a fine suspension in water and thus applicable by spraying or dipping. Some dusts are directly wettable by the nature of the dust diluent, among them various kaolins, but others must be made wettable, and thus suspendable or dispersible in water, by adding detergent or wetting agents.

These five general classes, then, represent the more common formulations in which insecticides appear. They suggest, as may be readily surmised, various methods and instrumentalities for their application under particular circumstances. Such instrumentalities may range from the humble hand sprayer or primitive sprinkling device to elaborate fog and mist or spray-generating machines or aircraft especially adapted for insecticide dispersion. Fumigants, too, may be formulated in simple ways. For example, a certain proportion of carbon dioxide may potentiate such a fumigant insecticide as methyl bromide and cylinders under pressure may contain appropriate mixtures of these two substances.

A few other general terms appear often throughout the book; if not otherwise defined, most of these are defined operationally in the text. However, few of these general terms, among them synergist, repellent, acaricide (= miticide), pediculicide, attractant, ovicide, have a special status in that certain compounds appearing as section titles belong to classes of substances for which these terms are designations. They are defined briefly here.

A synergist is, in our sense, a chemical compound which, while itself only slightly insecticidal or even non-insecticidal, when used in association with some insecticides (chiefly the pyrethrins) greatly enhances the toxic power of the mixture (insecticide + synergist) beyond the sum of the individual toxicities of the substances in the mixture. The phenomenon of toxicity enhancement by the synergist is referred to as synergism, activation, or potentiation.

A repellent is, in our sense, a chemical compound which although itself not insecticidal, or but mildly insecticidal, makes offensive or unattractive to insects a habitat, a food plant or an animal host or other food object ordinarily sought or frequented. Repellents are customarily narrow in their action, being active in the case of only one kind or at best a few kinds of insects or related arthropods. Oil of citronella is an insect repellent of respectable antiquity.

An attractant may be said to be the exact opposite of a repellent in its action. An attractant, in our sense, draws or attracts an insect to a situation harmful or lethal to itself. The situation may be a poisoned bait, a trap, a surface treated with a powerful insecticide, etc. The attractant is presumed to act at a distance primarily by olfactory stimulation. However, purely physical attractants, for example light, sound vibrations in a certain frequency range, etc., are also known.

An acaricide is a chemical substance which shows a potent or even a specific toxic action against those insect-related arthropods which belong to the class Acarina. Among the Acarina, or acarines, are the arthropods commonly called ticks and mites. The mites encompass many genera and species of acarines which are phytophagous or plant-consuming (by sucking of the juices, chiefly) but also many genera and species which feed upon or parasitize the bodies of many animals both vertebrate and invertebrate—a type of acarine which may, thus, be termed zoöphagous. Acaricide is a term to be preferred to miticide, commonly used as a synonym or equivalent, because acaricide implies activity against acarines—a natural group of arthropods—while miticide would imply activity limited to mites. Perfectly good insecticides may also be excellent acaricides and vice versa. Nevertheless, there apparently are between insects and acarines physiological differences sufficiently striking and deep-rooted that certain chemical compounds are particularly effective toxicants for the latter and not for the former.

A pediculicide, in a strict sense, is a chemical compound effectively toxic—and even specifically toxic—for lice.

and those lice members of the genus Pediculus, to which belong the lice of mankind with the exception of Phthirus pubis, the crab or pubic louse. By extension, pediculicide means louse-killer and, if we must coin words with a range so limited, let us be spared such an etymological crime as "lousicide"—a term which some have had the brass to introduce.

Ovicide refers to substances which kill eggs. In the context of this book, however, an ovicide means a compound particularly toxic to the eggs of insects or acarines.

Since the index of such a book as this is of prime importance and by its nature a key to each part of the book as a whole, a few words will be given to the index in this consideration of form as it applies to substance. Also the index is considered here because the author discerns an error of judgment which would have proved too great to repair without additional delay of several months and a marked increment in the cost of production.

The index of the book is in two parts. One part is given over to an alphabetical listing of all chemical compound names appearing anywhere in the section headings or in the text. The second part lists the common and scientific names of all the species mentioned in the text, with the exception of the common laboratory and domestic animals which appear repeatedly under the heading, "Toxicity for Higher Animals" in each compound section. Reference is made in both parts of the index not to text page number but to the section number, it being recalled that there are one hundred and eighty-eight sections. Many individual sections are indeed quite short, made up of a few pages—from one to three at most. In these instances reference to section rather than to page may be justified since the text is in such a form that the finding of a particular item within the section is easy enough. However, some sections are quite long. In these, discovery of a particular item from the index will be harder. The system, clearly, does not take it into account that a single item may be mentioned in more than one place in any given section. The system was adopted because it was expected that the sections would be reasonably short—which most are. Some excuse for the system lies in the fact that since each section is in itself a complete treatment of the toxicity (and related) data for each compound dealt with it was thought that the interested reader would deal as a whole with the matter offered in each section. Also, the generic and specific names of plants and animals, wherever they appear in text or table, are underlined to make them stand out. The system of indexing as a whole grew from the fact that the index was made up during the critical proofreading of the manuscript text in the interest of speeding publication of the book.

The internal structure of the index in each of its parts is simple. Nevertheless, chemical terms always present special and peculiar problems. In this instance such parts of chemical names as bis-, bi-, di-, cis-, trans have validity in alphabetical ranking of terms. However, symbols for meta-, ortho-, para-, namely m-, o-, p-, whether appearing at the beginning of or internally in a term are not valid in alphabetical listing but are respected in the internal ranking of stereo-isomers if more than one are mentioned. Thus m-cresol, o-cresol, p-cresol would all be listed under "C" at their appropriate place but with respect to each other would be in the alphabetical order of m-, o-, and p-. The symbols d-, l-, and dl- for dextro-, laevo-, and dextro-laevo- also have no significance in primary alphabetization of a term.

Symbols of chemical elements appearing as components of complex compound names, for example, symbols for nitrogen, oxygen, phosphorus, selenium, sulfur (N, O, P, Se, S) are ignored in primary alphabetic listing of a term whether present at the beginning of a term, internally within the term, or both. The symbol for normal, n-, the designations primary, secondary, tertiary, symmetrical, asymmetrical, or their abbreviations pri-, sec-, tert-, sym-, asym- (as, for example, in n-butyl alcohol, tertiary butyl alcohol or tert.-butyl alcohol) are ignored in alphabetic placement of a term. The various butyl alcohols appear in proper sequence under "B" and if several appear there together, with respect to each other, they are ranked in the sequence: n-butyl alcohol, sec.-butyl alcohol, tert.-butyl alcohol. Arabic numerals occurring at the beginning, internally, or at the end of chemical terms have no validity in alphabetic listing, but are respected in the arrangement, with regard to each other, of compounds whose designations differ only in the arabic numerals. To cite some examples of these usages: such compounds as 2,2-bis-(p-chlorophenyl)-1,1-dichloroethane and bis-(dimethylamino)—fluorophosphine oxide would appear under the alphabetic heading "B" and be ranked appropriately under it by the letter (s) following the prefix, bis-, which each of them bears, the 2,2- and p- and -1,1- of the first being ignored. However, 1,1-bis-(p-chlorophenyl), etc., would precede 2, 2-bis-(p-chlorophenyl), etc., if both were listed. Also, di-(p-chlorophenyl) methyl carbinol would be found under "D" in its proper place and would precede—the p- being ignored—dicyclohexyl-ammonium, 4, 6-dinitro-o-cyclohexylphenate and dieldrin. d-Nicotine, dl-nicotine, l-nicotine would be alphabetized under "N" as nicotine but listed in the order given with respect to the polarimetric prefixes. O, O-Diethyl-O-2-(ethylmercapto)-ethyl thionophosphate appears under the alphabetic heading "D" in its appropriate place as do O,O-diethyl-S-2-isopropylmercaptomethyl dithiophosphate and O,O-diethyl-O-(2-isopropyl-6-methyl-4-pyrimidyl) phosphorothioate, listed in that order—O,O-, -O-2-, -S-2-, -O- being ignored. Of course, S, S-diethyl-O-2-(ethyl mercapto)-ethyl thionophosphate, if such a compound existed and were mentioned here, would appear under "D" but would follow in the listing its congener, O,O-diethyl-O-2-(ethylmercapto)-ethyl thionophosphate. 2, 4, 5, 4′-Tetrachlorodiphenylsulfone appears in its appropriate alphabetic place under "T"—the 2, 4, 5, 4′- being ignored—and it properly precedes tetrachloroethane. Letters of the Greek alphabet likewise are ignored in primary alphabetization. Thus β-methylallyl chloride appears under "M", succeeding methoxychlor and preceding methyl bromide.

The method of bibliographic citation and reference also has validity for the work as a whole. There is a cumulative, alphabetic list of more than 3400 references at the back of the book wherein the listing is by author(s) followed by title of book or treatise or name of periodical, volume, page number and year. The bibliographic reference numbers in the text range from 1 to 3400-odd and a reference number may appear over and over again wherever appropriate. The reference numbers as they apply to any fact, statement, numerical value, formula, chemical equation, table, etc., are set off marginally directly to the right of the matter for which they are the source. Since the text is arranged in an outline form, juxtaposition of text material and reference number(s) is direct. If a reference number (or numbers) appears alongside a fact or statement from which depend subsidiary details, statements, interpretations, etc., the reference(s) given for the leading statement remain(s) in force for unreferenced subsidiary material until a new reference number appears marginally in sequence at the right. In tabulations which bring together facts or values from many sources, each line of data carries its appropriate reference number(s). In the case of statements, interpretations, etc., which combine material from several sources, all the reference numbers of the appropriate sources are set down in the margin. Introductory statements such as head most sections under the subtitle "General", may give, to the right of the word "General," a number of references which comprise the authority for the remarks gathered there as a *precis* of descriptive, historical, and other generalities relating to the subject of the section. Some of the physical and chemical data, coming from various standard handbooks which are themselves compendia from many sources, remain "unreferenced." It seems hardly necessary to cite an authority for an atomic or molecular weight, a specific gravity, a melting point, or the shape of a crystalline structure unless there exists discrepancy or controversy with respect to such parameters. Thus, to sum up, any statement or value may be traced to its source even though, in many instances, this may rest in several references. Primary or original references have been sought as much as possible but not with exhaustive pedantry. Other treatises, compendia, and "review articles" or "annual review" type books have not been eschewed as sources.

Numerous symbols, abbreviations, and shortcuts devised *ad hoc* have been used. Save where the meaning is clearly obvious from context they are explained or defined in a brief section titled "Symbols; Abbreviations; Definitions." Such mixtures of words and chemical symbols as nicotine 2HCl for nicotine dihydrochloride, nicotine SO_4 for nicotine sulfate, ethylene Cl_2 for ethylene dichloride or 4,6-dinitro-o-cyclohexylphenol Na salt for 4,6-dinitro-o-cyclohexylphenol sodium salt or sodium 4,6-dinitro-o-cyclohexylphenate—while admittedly bad etymologically and aesthetically—have been used to save space in tabulations and text. Although the author deplores the disease of alphabetic designation exemplified by DNA, ATP, ChE, ACTH, etc., he has bowed to the necessity of space consideration.

The author greatly regrets that the multiple reference numbers are not arranged in correct numerical sequence and that there are also some lapses from alphabetical listing of the names of insects in tabulations; most of these lapses resulted from late additions of data to the text which, for various reasons, could not be resolved by rearrangement before printing.

A perusal of a representative number of the sections of the book,—in particular the sections given over to exhaustive treatment of individual insecticidal compounds—will show that, throughout, a generally consistent form has been used for the presentation of data. Many aspects of the form are self-explanatory or self-evident. Others may require interpretation, in general terms, from various stand-points. The form of each section will not exactly follow that of all others because data for one compound which would appropriately appear under a certain heading (for example "Phytotoxicity") may be entirely lacking or the heading may be inapplicable. In such a case the general topic "Phytotoxicity" would not figure in the treatment of the particular toxicant. On the other hand, for another toxicant the topic "Phytotoxicity" may be very apropos, and data upon that subject abundant. In still other instances where data on phytotoxicity would appear distinctly apropos but are, nevertheless, lacking in any precise form, the heading "Phytotoxicity" may appear with the statement that no data are available to the author or with the indication that general application to living plants for insect control indicates that at insecticidal levels the compound in question is innocuous, at least, for some plants.

After the statement of the title name of an insecticide, the listing of its synonyms, the presentation of the structural formula and molecular weight, a section customarily headed "General" gives generalities concerning the substance, its history, special abilities or disabilities it has shown in use, summary avaluations of the hazard involved, special warnings and precautions, etc. At this point a compound is characterized in brief without the presentation of precise or quantitative data.

Directly following the "General" material, physical and chemical data concerning a compound are given. These may include general description of the color, physical state, odor, taste, crystal type (if any) of the compound and may indicate any notable differences of properties existing between the substance in a state of high purity and as a technical or commercial chemical. Important physical data on melting point boiling point, specific gravity, vapor pressure, polarimetric properties, refractive index, etc., are given, if available. Many of these data offer valuable hints on stability, persistence, and other properties. Marked attention is given to solubility; in many cases extensive tables of solubility of a compound in a wide range of solvents are supplied. This is of value as a guide to solvents suitable for concentrates, to alternate solvents which may be substituted for some which are unsuitable for reasons of toxicity, inflammability; and so on. If available, data relative to the stability of a compound in various forms and in solution are offered, with indications of halflife as a guide to possible residue hazards and time limitations of use before harvest of crop plants. Various chemical information may be listed, including such aspects as methods of synthesis, reactions undergone with various solvents and formulation additives and hydrolysis constants at various degrees of acidity or alkalinity as measured by pH. In the case of various fumigant liquids or solids data are given, if available, on the amount of the substance which may be expected to exist as a vapor in air in a stated volume under various conditions of temperature. Information on the most usual types of formulation in which the compound is used are presented. Data comparing a given compound physically and chemically with closely related compounds are emphasized when available and apropos.

The general heading "Toxicological" covers data which are most pertinently concerned with the toxicity, quantitative and qualitative, mode of toxic action, biochemical, physiological, pharmacological and pharmacodynamic properties of the compound, hazard, chronic toxicity as revealed by long-term feeding and/or exposure tests, and numerous other aspects which may be apropos generally or to a specific substance particularly. However, for simplicity, the data on toxicity included under the heading "Toxicological" are divided into three general parts: "Toxicity for Higher Animals" in all its quantitative, qualitative, acute, chronic and comparative aspects; "Phytotoxicity", similarly considering properties toxic for plants; and "Toxicity for Insects" under which are grouped, as for higher animals, quantitative, qualitative, comparative, and other data. Comparisons are made at every point where these are possible and useful. Under the general topic heading "Toxicological," special stress is given to facts and indications on hazard or toxicity for wild and game animals, terrestrial and aquatic, and for useful and beneficial insects.

The subject of the appearance of resistance to insecticides by several insect species after exposure to toxicants experimentally or in the field is dealt with as a special facet of the general physiological action of these agents. Resistance developing toward a particular toxicant is treated in the section for that compound. One general section is devoted to the fundamental subject of "acquired" resistance. Quantitative evidences of developed resistance are provided in numerous tables that deal comparatively with various strains or biotypes within an insect species in terms of such measures of relative toxicity as the LD_{50}, LD_{95}, etc., and measures of relative resistance.

Quantitative toxicological data are set forth in two complementary arrangements. This applies to each of the three general groupings of the toxicity data, namely as they relate to higher animals, plants and insects. The first of these arrangements presents grouped quantitative data of diverse origin; the second avoids such combination of data and presents data derived from one worker or group.

Under the first type of arrangement, many species are listed together sequentially in a tabular form which: provides, in general, for specification of the "route" or avenue of application of the toxicant, for example oral, sub-cutaneous, intraperitoneal, topical, inhalation or fumigation, as contact spray, contact dust, contact with a residual deposit, etc.; provides for the "dose" (as a characterization of type of dose) for example, LD_{50} (median lethal dose), LC_{50} (median lethal concentration), LD_{100} (dose yielding 100 per cent mortality), MLD (minimum lethal dose); provides for statement of "dosage", i.e., the quantity of toxicant given in stated units (micrograms, milligrams, grams, etc.) per unit of body weight (kilogram, gram, milligram or per individual organism) preferably with individual weight or average weight stated; provides a special place or column for "remarks" whereby special conditions or circumstances relative to each line of data may be given in brief. The column given to "remarks" may list, among any number of factors, such indications as exposure time, temperature during treatment, holding temperature after treatment, time of death after administration of a given dosage, vehicle or solvent, special symptomatological signs, age and condition of tested organisms, or any other useful information.

These tabulations not only group together data gathered about diverse organisms but also data derived from many sources by many methods, as the remarks and line-by-line references testify. Thus, specification of method, route, formulation, experimental circumstances, etc., is all-important in accounting for and interpreting the large variation which may be shown by data referring to one and the same species, whether this be a higher animal, an insect, or a plant. It will be apparent, the author believes, that pains have been taken, within the limits imposed by tabular method, to set forth concisely—even to the sacrifice of formal grammar and the invention of many abbreviations—pertinent circumstantial details.

The second arrangement or guise under which quantitative toxicological data are offered avoids the grouping of data from diverse sources. It reproduces directly—or in a form modified as stated in the legend—facts which derive from one worker or from collaborating workers and which ordinarily relate to but one or a few species. Such tabulations make it feasible to give more precise and full statements of experimental conditions, methods, number of replicates, statistical tests of validity, etc., than is permitted by tabulations of grouped quantitative data.

Much less opportunity for successful tabulation is given by the results of long-term feeding or exposure tests intended to measure chronic effects, accumulation in tissues, residue problems, hazard for species other than those for which the toxicant is made and, generally, effects other than those gained from tests of acute toxicity. The same is true for descriptions of various pathological manifestations, symptoms of intoxication, danger signs of toxicant accumulation in the body, histological and histopathological information, descriptions of precautionary measures, and a host of other useful and instructive indications. In the presentation of these, form has been fitted to content in many ways—chiefly semi-tabular and outline, with a heirarchy of topic headings, titles, sub-titles, etc., as may be readily appreciated by a glance at any of the longer sections and more than twenty sections devoted to "general treatments."

Wherever pertinent data are available, prominence is given to the mode whereby a toxicant generally enters the bodies of diverse living organisms and to the fate of the toxicant after entrance. By and large the most prominent methods for the application of insecticides, especially in agricultural use, are those which disperse the toxicant as a liquid spray or dust over a standing crop or the natural vegetation harboring the pest insects. Emphasis, if one may generalize, is on contact toxicity. This brings into prominence the nature and properties of the insect integument. These methods emphasize also the hazard present for creatures other than insects which may simultaneously be exposed to the insecticide. The manner whereby the insect integument mediates or impedes the entry of a toxicant into the body, the influence upon passage or failure of passage of the physical state of the poison, the nature of its formulation, the effect of solvents, of the abrasive properties of dust diluents, the thickness or degree of sclerotization of the integument and the nature of its constituents, its lipid or lipid-like or proteinaceous coats—a host of factors, structural, physical, chemical—have been the subjects of a multitude of investigations, speculations and theories.

This book does not attempt any detailed consideration of the insect integument. Still the proper interpretation of the data on contact toxicity, residual sprays and dusts, dipping experiments and dip insecticides, etc., must irresistibly draw attention to the subject of the insect integument. From the viewpoint of their bearing upon the methods and evaluations used in insecticide testing, the properties of the insect integument have been rev ed admirably by W. M. Hoskins in a recent collaborative volume edited by Harold H. Shepard and published by the Burgess Publishing Company (1958) entitled *Methods of Testing Chemicals on Insects, Volume I.*

Insecticides are pre-eminently for practical use and chiefly for use by the non-specialist. In planning this book it appeared important not only to deal with laboratory tests, but also with the precious body of data gathered from the practical field use of insecticidal chemicals, or from large scale field experiences mounted as controlled experiments but subject, naturally, to many more variables than surround the laboratory test. Many of the sections—particularly those having to do with recently developed insecticides already in use on a vast scale or with older toxicants long in use—close with a general tabulation briefly recording results or evaluations from field experiences. Such experiences give important indications of the relative merits of various insect toxicants but all judgements must be qualified strictly by the consideration that these experiences are specific and to be interpreted in the light of the variables and circumstances which are integral elements of each. A substance in controlled laboratory tests may show itself to be supremely effective as an insect toxicant for one or many species yet, if field experiences under a wide variety of naturally occurring conditions shows it to be less effective in practical insect control than a substance of lesser absolute toxicity, it must be accounted of less practical interest than other toxicants. Since a brief tabulation or *precis* cannot take account of the all-important variables and field circumstances, conclusions of the relative merits of insecticidal products should not be grounded on these indications. Such judgment should be based on the full reports.

Nevertheless, the results collected in laboratory and field have an inescapable relation. In the laboratory the methods of insecticide testing have been, and are being, progressively refined in terms of methods of controlled, effective, properly measurable application of the toxicants, among other improvements. The maximally effective use of an insecticide in the field often involves the adaptation of methods and instruments which have proved effective in laboratory toxicity tests. Precision spraying or dusting, for example, are as much to be desired in the field as they are essential in the laboratory in critical, quantitative evaluations. At the same time it should be remembered that an insecticide applied to orchards or grain-fields covering square miles by elaborate airborne devices may be used also by a horticulturist or floriculturist in a simple hand-pumped sprayer or duster.

The test of field effectiveness of an insecticide, properly applied, is full practical control (of which the optimum is, of course, elimination of the pest insects) with a minimum of danger to the user and to plants and animals. Measurements of toxicity (and thus partially or indirectly of effectiveness) made in the laboratory may use different terms or be based on quite other values. Yet, laboratory tests of toxicity tend naturally toward the determination of a practical insecticide, whether or not this is the goal. The LD_{50}, or median lethal dose, statistically speaking, for an insect form under specific conditions, may tell quite as much, and in terms as welcome, to the scientist in his laboratory as the complete elimination (LD_{100}) of a destructive pest from his field or garden achieved by that substance tells the practical user. The point is, simply, that one must not leap to conclusions solely on the basis of laboratory median lethal dose values.

The measure of toxicity most frequently employed in this book is the median lethal dose (LD_{50}) defined under specific experimental conditions, or parameters closely related thereto, such as LD_{95}, LD_{100}, LC_{50}, LC_{95}, LC_{100}, etc. This entails the need to say something about these measures of toxicity, and indirectly of effectiveness, and the methods whereby they are obtained. The methods, it goes without saying, must be appropriate, properly controlled and standardized in as many details as possible. The measures of effectiveness evoked by the methods must likewise be meaningful and subject to statistical verification of their significance.

The results or data derived from tests of toxicity are arranged, nowadays, generally in the form of a dosage mortality curve. Such a curve plots the mortality achieved in a stated period of time by a given dosage of toxicant per given unit of body weight of the test organism. A sufficient series of graded dosages (the results of which are recorded in terms of mortality per cent) yields a curve sigmoid in shape. The nearing of the asymptotic by a curve of such form to the areas of one hundred per cent mortality at one end and no mortality at the other is hard to measure and define. To find with accuracy the LD_0 and the LD_{100} calls for great replication of tests performed on large numbers of test subjects and even approximation of these values is hard indeed. In estimating them one must rely on the limited number of test individuals dying in the lower dosage range and the correspondingly few surviving in the higher dosage range. Thus individual peculiarities and idiosyncrasies become over-riding. It is far easier and more accurate to discern the dosage which yields the death of one half the number of test subjects. So, in comparisons of toxicity among substances and in determining its corollary, the differences in susceptibility to a toxicant of various species, age groups, life-cycle stages, etc., the median lethal dose (LD_{50}) has been all but universally adopted. For laboratory and domestic animals, and for vertebrates in general, dosages are expressed most commonly as milligrams or grams of toxicant per kilogram of body weight. In the case of fumigants, the median lethal concentration (LC_{50}) is generally used and is most often expressed as milligrams of toxicant per liter of air, although it may also be stated solely or supplementally as parts per million (ppm).

Some experimentalists, notably H. H. Shepard and his collaborators *(Minnesota Agricultural Experiment Station Technical Bulletin No. 120, 1937)* have taken exception to the use of the median lethal concentration value as a practical measure in testing comparatively fumigants for insecticidal power. By extension, their criticism may also be levelled at the LD_{50} generally. They have offered reasons and means for finding with statistical validity dosage values yielding more nearly complete kills of the test subjects, bringing forward argument in favor of the LD_{95} as a more practical ground for comparing toxicity. Many workers in this field report various values in their papers, for example LD_{25}, LD_{50}, LD_{75}, LD_{95}, LD_{99}.

In any case present-day tests of acute toxicity are made by applying series of graded dosages or concentrations of toxicant which yield a range of mortality values between 0 and 100 per cent of the number of test subjects. Values so obtained may be treated according to formulae and methods generalized by W. S. Abbott (*Journal of Economic Entomology 18:* 265-267, 1925). By probit-logarithmic transformation of the statistically corrected dosages and mortality per cent values the sigmoid dosage-mortality curve gives way to a dosage-mortality plot of straight line character. From plots of this type the dosages or concentrations of toxicants which may be expected to yield various percentages of mortality among the test subjects can be very well approximated. Details of method and of mathematical treatment logically applicable to comparative toxicity determinations have been provided, among others, by C. I. Bliss (*Annals of Applied Biology 37:* 508-515, 1935), F. M. Wadley (*American Association for the Advancement of Science, Publication 20,* pp. 177-188, 1943), and D. J. Finney (*Statistical Treatment of the Sigmoid Response Curve,* Cambridge University Press, 1952, second edition). Workers quantitatively testing the acute toxicity of fumigants have been for many years notably sedulous to apply careful statistical procedure and proper validity tests to their data. More recently the papers and treatises of experimentalists dealing with the toxicity of agents other than fumigants have shown increased care to state explicitly the methods whereby data have been obtained and statistically treated. Increasingly, they provide the experimental ranges of the values, standard deviation, standard error, least significant difference and other aids to interpretation of their findings.

However, standardized and accurate methods of applying or administering insecticidal substances to test insects with regard for proper controls are not as old, by any means, as are many and quite voluminous data on toxicity of insecticides, particularly those insecticides which came into general practical use during what might be called the "ancient history" of insecticides. Nowadays, and in the quite recent past, methods of exceptional ingenuity and relative ease of application have been (and continue to be) elaborated. Such methods facilitate accurate laboratory evaluations of insecticide, and would-be-insecticide, toxicity upon insect subjects. These methods show increasingly high refinement and subtlety. In miniature, of course, they reflect all the modes whereby insecticides are now applied accurately, economically, and with maximum effect on the grandest practical scale. In addition to these, delicate methods of local application to and injection into insects have been devised for purely laboratory evaluations of toxicity and mode of action. Such methods have kept pace with, and added much to, the advance of knowledge of insect physiology and biochemistry. There are, then, at hand various methods for controlled topical application and injection of insecticides to insects, precision dusting, spraying, dipping, feeding and drinking methods, ways of testing fumigant action, residual action, systemic action, effects of respiration, on enzymes and enzyme systems, on tissue microanatomy, etc. Each has its special virtues, appropriate controls, peculiar pitfalls, just as each has its proponents. All the more important, therefore, is the need to specify method and to bring forward the results of many methods in gathering general data on insecticide toxicity. Much less definite and less well explored in insecticide toxicity tests is the part played by "randomisation", sampling, and inspection or observation of test subjects during and after treatment in affecting the results achieved. It may be expected that these are factors of some importance, being among those elements of the experimental procedure that should be specified. Rarely, however, does one find them explicitly set forth.

Some general explanation of the more common methods of insecticide testing is appropriate. The unavoidable brevity imposed by the nature of the text on indications of experimental method may have made these rather cryptic. Many will ask, no doubt, what is meant when it is stated that a compound was tested upon a certain insect by application according to a certain turntable method, by some settling tower technique, by dipping or rolling or by a vacuum dusting process. Descriptions and explanations which can be given here will still not be complete. They cannot absolve the reader from looking into the reference sources for detailed descriptions if he feels need of these. Even for any general method of insecticide application there may be numerous modifications of procedure and much variety in instrumentation.

The exhaustive field test only can give the final evaluation of an insecticide in all its aspects, and of its toxicity for insects in particular, as this is reflected in the degree of control obtained. To this ultimate test, laboratory testing, carried out with high precision of method and yielding results readily reproducible, is an indispensible prelude. What follows in outline form is a short resume of general methods presently in use in insecticide testing:

I) Topical application; direct injection:
  a) This method, which is very much to the fore at present, involves the controlled administration of toxicant in critically measured amounts, and ordinarily in suitable solution, directly to the surface of individual insects. Clearly it is a laboratory method primarily, but equally clearly it can have much to contribute to field applications of insecticides in the form of finely divided and dispersed droplets having toxicant in solution, emulsion or suspension, in the form of dusts of rather uniform particle size or as residual deposits where contact is relied upon to poison the insect. Attention is drawn to the brief section 105 of the text which offers data on spray droplet behavior.
    1) Application is made ordinarily as single drops placed upon or spread over particular chosen areas of the insect body. Thus, drops may be placed on the pronotum, on the cervical membrane, sternally or intersternally, near or far from the central nervous system or, indeed, at any chosen site. This permits evaluation of differences of susceptibility or sensitivity of the insect, if any such exist, which depend on site of application, degree of sclerotization of the integument, presence or absence of natural lipids, waxes, cuticular deposits, influence of abrasion, etc.
    2) Droplets can be delivered with precision by using needles of fine bore, carefully calibrated micrometer syringes, and various holding devices or means of anaesthesia.
  b) Much the same equipment and methods can be adapted to inject directly into the insect--under the integument, into various members, into heart, blood or other organs, into mouth or stomach--measured amounts of toxicant.
    1) Minute amounts of toxicant may be measured out by precise but essentially simple instruments. Such quantities as 0.001 to 0.01 micrograms may be delivered in small volumes of solvent or suspending fluid, for example, 0.1 to 1.0 microliters.
  c) The foregoing methods permit also consideration of the part played by various solvents in mediating or modifying the action of insecticides.
    1) Toxicity of various organic solvents such as acetone, dioxane, alcohols, etc., may be evaluated, and the part played by solvent volatility or non-volatility, as well as many other factors, may be evaluated.
  d) Topical application or direct injection of precisely-measured and minute quantities of toxicant allow the testing of finely-graded dosages and the use of criteria other than death in studying effectiveness,

for example, doses effective in yielding particular degrees of immobility or paralysis, tremors, behavioral alterations, heart rate changes alterations of nerve action potentials, etc.

e) Topical application and injection methods are succinctly reviewed with excellent detail and bibliographic references by R. L. Metcalf in H. H. Shepard's *Methods of Testing Chemicals on Insects Volume I,* Chapter VIII, Burgess Publishing Company, 1958.

II) Feeding and drinking methods:

a) These are the methods which come immediately to the popular mind when considerations of poisoning are brought up. Such methods of testing are a *sine qua non* for toxicants which act as "stomach poisons" upon ingestion, whether this be their sole route of effective entry or one of several routes of entry into the insect body.

1) The methods are legion and many are extremely ingenious. They have been reviewed in detail by F. W. Fisk in chapter IX of the reference cited above.

b) The test insects may have unlimited access, by feeding or drinking, to the toxicant which may be made constantly available in the food and drink by various ways. The toxicant may be mixed in or placed upon suitable food which is present in the holding cages or devices. The insects may be living in, or placed directly in, a medium in which the toxicant is present, for example: in the rearing media for fly larvae; adsorbed or absorbed by textiles in feeding tests for clothes moths, etc., in grains, flour, dried fruits and other stored products which form a habitat for the insect, for example, grain weevils; in baits rendered attractive to the insect in one way or another. The toxicant may be in liquid sirups or in fluids like plant juices or blood, drunk through membranes which simulate natural feeding situations.

c) The toxicant may be offered or administered to the insect by limited dose feeding. The toxicant may be offered in the form of deposits, pastes, coatings, etc., on the fresh leaves of suitable food plants, placed in measured amount on suitable squares or discs of acceptable leaves, as "leaf sandwiches" with the toxicant between two pieces of suitable leaves, in pellets such as bran baits. Or the poison may be given in measured doses in liquid media placed on the mouth parts, in the mouth, or introduced into the foreparts of the gastrointestinal canal.

d) These methods may be adapted as large scale semi-field tests by placing insects in large cages placed over natural food plants growing in pots or open soil and suitably treated with toxicant by various methods of spraying, dusting, coating, etc.

e) All of these tests and methods, however, carry very arduous conditions connected first with the deposit of the toxicant on the material to be eaten in measured, evenly distributed amounts so that the amount taken by the insect can be accurately measured. This may involve various planimetric techniques to discover the area eaten of such things as coated leaves so that the dosage may be estimated in terms of a known rate of deposition of the toxicant, and require delicate and time-consuming direct weighing methods, scanning methods, etc. In such feeding experiences the methods worked out for precision spraying and dusting have direct applicability as means for precise distribution of toxicant over surfaces of leaves or plant parts. Questions of natural dietary and of normal feeding habits and optimal feeding conditions are involved and play a great part in correct interpretation of results.

III) Dipping methods:

a) These methods which involve the immersion of the test insects, usually in groups or batches, in aqueous or other solutions, emulsions, suspensions, etc., of the toxicant for measured short periods really form a special case of topical application.

1) Closely related to dipping methods are those tests in which insects are rolled or shaken in dust dilutions of the toxicant or allowed to enter *ad libitum* parts of the environment over which the insecticide in suitable formulation has been dusted.

b) Plainly, the dipping and related methods are far less precise and susceptible to exacting measurements of dosage. Also it is difficult to rule out the ingestion of toxicant during the dipping process, if it is the contact effect that it is desired specifically to measure. The grooming habits of the test insects, whereby surface-applied materials are swept off by the mouth parts, are likewise to be considered.

1) Very important also becomes the treatment of the insect after its immersion—how it has been dried, whether excess moisture is blotted off, freedom of the holding cages from deposits of toxicant due to excess solution or suspension shaken from the insect surface, and a host of similar factors.

2) Consideration of harmful effects of the immersion procedure as such is necessary and such effects should be ruled out or allowed for by various refinements of the method.

c) In spite of apparent lack of precision and the presence of variables hard to control, dipping tests using adequate numbers of test subjects show a good order of reproducibility in terms of results, considered from a quantitative standpoint of dosage, exposure time, holding conditions, and so on. It is essential to administer carefully to control subjects all the treatments and manipulations undergone by the experimental subjects, save the exposure to toxicant.

1) At play here are all the factors which must be taken carefully into account in other insecticide testing methods and which should be specified in reporting results. These include: age, sex, life-cycle stage of the test subjects, nutritional state, immersion time and immersion temperature, post-treatment holding temperature and humidity, reaction time, time allowed before reading of results so that recovery from adventitious effects, such as temporary anoxia as a result of immersion in liquid, may take place.

d) Dipping methods have been reviewed in detail, and bibliography compiled, by A. H. McIntosh in chapter X of the Shepard reference previously cited.

1) Evaluation of toxicant effect after dipping application, clearly has much to indicate in terms of insecticides practically applied by this method, for example, in cattle, sheep, poultry and other dips for control of lice, ticks, mites, flesh flies, etc.

IV) Precision-spraying methods:

a) These methods as applied in the laboratory for insecticide evaluation are related directly to one of the major and universal methods for applying insecticides on a practical scale. The general methods of precision spraying are few, but special modifications and nuances are legion. They have been summarized in considerable detail and with an excellent bibliography by C. Potter and M. J. Way in chapter XI of the Shepard reference cited above. Spraying, of course, involves the dispersion by suitable instruments of a toxicant in solution, emulsion or suspension, as a cloud or mist of droplets relatively course or fine. Having created the spray or mist by suitable means, it may be applied to achieve several purposes:

1) To apply equal, similar, or comparable doses of toxicant directly to the body surface of the text insect. Plainly, this touches closely upon the methods of topical application.
2) To scatter or distribute a measured dose of toxicant in suitable solution, emulsion, or suspension over a surface area as a residual deposit with which test insects may afterward come, or be placed, in contact.
3) To distribute evenly and uniformly over the surface of something to be eaten by an insect—leaves of a food plant, other plant parts—a given dose of toxicant. This last application is done with more precision in the dispersion or distribution of stomach toxicants by settling mist methods and apparatus than by direct spraying.
4) To distribute a stated dose of toxicant uniformly over the natural habitat of the insect, or replica thereof, or over a food plant growing in field or container. This last purpose impinges upon, or merges with, the practical spray application of a toxicant when it is done with nozzles and pumps of high precision. Evaluations gained by methods so closely approaching the practical are less exact and require more judgement and discrimination for good interpretation.

b) A multitude of instruments and arrangements of instruments has been devised to achieve best, most accurately, and most directly the various purposes stated. Instrumentalities for both spraying and settling mist arrangements have been specialized for most efficient direct application of sprays to the insect body, the application of deposits to surfaces, and for both these tasks.
   1) Virtually all the instruments, or instrument groups, devised for precision spraying or the production of uniform settling mists have in common, I) an atomizing, mist- or spray-producing nozzle, II) a chamber in which insect or surface may be exposed, devised in various ways to promote mixing, take advantage of turbulence, separate different ranges of droplet size into different regions, promote even settling or distribution, etc., III) some type of reservoir, tank or cartridge in which the measured dose is placed, or from which a measured dose may be drawn, and IV) a means of exposing various kinds of test insects—crawling, flying, resting, immobilized, pinioned, etc.,—for exactly-timed intervals, and in replicate groups, to the toxicant.

c) Space does not allow any detailed description of instruments or the nature of physical factors involved in precision spraying tests. Those interested will find the details in the Shepard reference cited and its bibliography.

V) Precision dusting:

a) What has been said about precision spraying applies with equal force to precision dusting. In these methods of toxicant application the problems are those of the precise, uniform, and reproducible distribution of substances in particulate form—relatively coarse or relatively fine, uniform or diverse in particle size, crystalline or amorphous, heavy or light. However, the physical characteristics of dusts are quite different from those of solutions, emulsions or suspensions in droplet form, and are less known. Toxicants in dust form are almost invariably diluted or formulated with inert dust diluents whose properties may be highly special.
   1) As in the case of liquid sprays, dusts are applied, depending upon the mode of action and toxic properties of the toxicant, to act by direct or by residual contact, as stomach poisons after ingestion in the form of deposits on food plants, or as a result of grooming by the insect of its dusted body, or to serve a dual purpose of both contact and stomach poisoning.
   2) Whatever the method of specific application of dust toxicants, the degree of precision in terms of even distribution, amount deposited, exact dosage determination, and other quantitative considerations is much less than in the case of sprays and settling mists. Nonetheless, reasonably reproducible results have been achieved.

b) Plainly, the degree of precision in method or evaluation to be achieved by rolling, or tossing, or shaking the test insects in a quantity of the dust toxicant is not great. Much less precision attends those methods which permit the insect to enter a dusted area of the habitat or environment *ad libitum*. Still, these methods have been used and much of the older, though still valuable, data for such insecticides as sodium fluoride, cryolite and derris has been gathered by these methods.

c) As in the case of precision spraying, the desire to achieve precision dusting has brought forward numerous instrumental arrangements to yield uniform dust clouds to produce uniform deposits in several kinds of dusting and settling towers or chambers. Dust guns here take the place of nozzles.
   1) The greatest degree of uniformity achieved in distributing a measured amount of dust toxicant has come by way of vacuum dusting methods which deposit dust uniformly on all exposed surfaces of insects, food plants, cages, etc., by the instantaneous breaking of a vacuum in an appropriate test chamber or vessel.
   2) Regardless of the uniformity achieved by the dispersing apparatus, the dusting method is only as good as the methods used after application to measure quantitatively the deposit on a given area of surface or the amount ingested by an insect in the form of coated discs or squares of leaf or as leaf sandwiches with toxicant dust fillings.

d) Precision dusting techniques and apparatus have been succinctly treated by J. E. Dewey in chapter XII of the Shepard reference previously cited.

VI) Tests of fumigant insecticides:

a) Section 104 of the text presents a general consideration of fumigant insecticides. In that section may be found descriptions in considerable detail of the methods and the factors important to tests of fumigant toxicity. In addition an elegant *precis* on this subject has recently appeared and the reader's attention is drawn to chapter XIII by R. T. Cotton in the previously cited Shepard reference.

VII) Miscellaneous:

a) There have been recent new departures in the field of insecticide application and insecticide action. Among these new departures is the introduction of the so-called "systemics" or "systemic" insecticides, the subject of section 172 of the text. These require for the evaluation of their action and potency new methods and quite subtle approaches. The use of synergistic agents in insecticide formulations has proved immensely valuable and new synergists may be expected to appear in greater number. Section 171 specifically treats of the phenomenon of synergism as it applies to insecticides. Methods for the testing and evaluation of synergistic agents are given there explicitly and implicitly in the operational sense. New horizons have been opened also by the appearance and increasing elaboration of organic phosphate or "organophosphorus" insecticides.

Since the mode of action of these agents seems strongly to center upon the inhibition of choline esterase(s), *in vitro* systems for studying quantitatively the inactivation of the enzyme(s) have been devised and are important in toxicity evaluations of this "family" of toxicants. Section 134 of the text treats generally with these particular agents. Radioactive tracer methods may also be expected to come to the fore in the future. No consideration specifically of radioactive isotopes in insecticide studies has been given in this work. However an interesting review of their application in insecticide studies is offered by A. W. Lindquist in chapter VI of the Shepard reference cited above.

There remains to be considered briefly some of the important factors and variables which are all-important in their influence upon the mode of action, the toxicity and, indeed, the general behavior of insecticides as this is manifested in laboratory testings and practical field uses. Without due regard for these factors and variables, experimental data may be subject to gross misinterpretation or improper emphasis. These factors and variables are among the details which this work has sought to indicate, however briefly, in the tabulations of the experimental findings. Without these indications the tabulations may too easily appear to be a disparate melange of values showing little regularity and less coherence. More experimentalists are now explicitly considering such variables and taking the measure of their influence upon the experiential data which their studies yield. Although all these factors and variables may be found throughout the text it may serve by way of introduction to set them down as a group and consider them briefly in general terms.

Information on the variables which derive from species specificity, from inherent species difference alone, (whatever may be the physiological or biochemical basis) as these relate to insects is scarcely tapped, much less well known. Out of the thousands and thousands of insect species—to say nothing of biotypes, strains, races, varieties, etc., within those species—only a handful has formed the material for experimentation and close scrutiny. In the toxicity tabulations of this work, run down the lists of generic and specific names and consider how the same old acquaintances show up again and again in endless repetition—Anasa tristis, Apis mellifera, Bombyx mori, Melanoplus differentialis, Musca domestica, Oncopeltus fasciatus, Periplaneta americana, Anopheles quadrimaculatus. There are good reasons why this is so. There are also abundant reasons to keep in mind how limited is the penetration of our exact knowledge into this world of extraordinary organisms. As new species and genera are selected as experimental material we may expect to see many generalizations shattered or provided with interesting exceptions. This is true generally in terms of physiology, biochemistry, etc., and specifically in toxicity studies and in the insect pharmacodynamics of insecticides.

In addition to the factors making for susceptibility or resistance to the toxic action of various insecticides which are inherent in the specific nature of insects—or, for that matter, any other organism—and dependent on the particular biochemical, physiological, genetic, and structural make-up of a genus, a species, a sub-species, a variety, a biotype, a strain or an individual mutant, there are other factors which alter the activities of toxicants. Since these factors play a very great part in the variability of data on toxicity and the nature of so-called standard values derived therefrom, it seems useful to review them here. It will be noted that, in the text and tables, wherever pertinent variables have been explicitly made known by sources used, these have been indicated. Indeed, some sections are given over wholly to consideration of factors making for altered susceptibility or resistance to insecticides, among these being section 173 on temperature and insecticidal action and section 156 on "acquired" resistance or "fastness" on the part of insects toward various toxicants.

The question of those phenomena associated with individuality or "specialness", whether this relates to an individual organism or the collective individuality of a species, is too all-pervading to be usefully illuminated by the brief treatment, however succinct, which could be accorded here. These factors we will accept as given—as being of the order of nature. Others are less subtle, less all-pervading, in terms of cause and effect, and may be noted or even briefly discussed here to some useful end. The author is guided here by the order of treatment followed by C. Potter and M. J. Way of the Rothamsted Experimental Station at Harpenden, Hertfordshire, England, in chapter XI of the Shepard reference frequently cited. The bibliography provided by these authors is altogether excellent. Much of this same bibliography the author has independently explored and the specific data are embedded in the text.

I) Instar, or life-cycle stage, and age of the insect within the instar or life-cycle stage:

Susceptibility to toxicants is influenced variously by instar, life-cycle stage, age, and sex of the test insect. The degree of influence exerted may differ widely with respect to diverse toxicants. Any one of these variables may increase susceptibility to one poison and decrease it toward another.

II) Nutritional state of the test subject(s); other nutritional factors:

The nature of the food and the amount in which it is given or received alters the response of various insects toward diverse toxicants. This holds true with respect to the dietary period before testing and in the holding period after ministration of the toxicant. Myzus persicae, for example, has shown measurably different response to nicotine, used as a fumigant, depending on the plant used for rearing the aphid, namely turnip, lettuce, climbing Dahlia, Nasturtium.

III) Place of application of the toxicant on the body of the test insect:

The general organization of the integument of insects is, of course, similar over the whole of the class, Insecta. However, the disposition, nature, thickness, waxiness, oiliness, glabrousness, hairiness, wettability, etc., of the cuticular layer of the integument alone, may differ sharply as between species, between life-cycle stages or instars, and between body regions. If the insect is or can be sprayed, for instance, over-all by an effective contact insecticide or toxicant these differences are not too important save as their algebraic summation may determine the overall effective dose. Quite different, however, is the situation in tests whereby the dose may be deliberately localized. And this fact achieves practical importance with regard to toxicants intended for use as residually toxic deposits or films. Susceptibility of the individual insect has been found to vary markedly depending upon the region of the body where a given test dose is applied. This may be manifested by difference in the LD_{50} of a given toxicant for different application sites, time required for the production of a given response—death or otherwise—and in many other ways. At any given place of application, the physical state of the toxicant, the solvent used, and the environmental circumstances attending the application may alter the result.

IV) Physical condition and state of the toxicant; vehicle or medium of application:

Especially in the case of a poison applied as a solid, either by contact or by mouth, do the particle size and nature of the crystal or shape of the particles affect the result in terms of the susceptibility or resistance of the insect. The type of vehicle or medium is of great importance as it enhances or promotes entry of the poison to the sensitive regions or systems of the test subject, makes the toxicant more palatable or acceptable, quiets or inhibits mechanisms which might effect the regurgitation of an intaken poison or promote or retard the rate of passage through the gut, synergizes with the toxicant, or in any way alters or affects the natural barriers to the entry of foreign substances. Thus, of course, the nature of a formulation may influence deeply the activity of any given insecticide. Surface active agents, pH of the medium, protective adjuvants added to retard degradation or alteration of the toxic molecule, all may affect the quality and intensity of the response of the test subject. In the case of contact poisons working as residual deposits, the texture or nature of the surface has an effect on toxicity both in terms of influence on the toxicant itself and the effect it has on the adequacy of contact of the test subject with the poisonous deposit.

V) Deposit level and toxicant concentration:

In the case of contact sprays, contact dusts, and residual deposits or films, made either by application of dusts, emulsions, suspensions or solutions, these factors influence toxicity as this is revealed by measurements of test subject mortality. Usually, when a stated volume of dissolved poison is administered, by direct contact or as a residual deposit, toxicity increase is a direct function of increased concentration of toxicant. Over the mortality range, or most of it, probit-mortality and log-concentration relation is linear when graphed. Oil-borne toxicants used as sprays yield an enhanced mortality with increased deposit level but this effect may not follow in the case of water-borne toxicants. The so-called run-off point of the solution, suspension, or emulsion may be such that any increase of amount applied beyond that point has no effect in enhancing the amount of poison held on the insect surface. In residual deposits, too, a level may be noted below which there is no response on the part of the subject, and a level above which no increase in toxicant deposit will enhance the response. With regard to this deposit range the nature of the surface holding the deposit is an important factor. Depending upon the particular toxicant, application in a concentrated or in a diluted form may yield an optimum toxic effect. Technique of application is a factor in this last consideration. In the case of tests by settling mists, dusts, and spray methods, particular attention must be accorded to levels of deposit and concentration.

VI) Exposure time; reaction time, or inspection time, or test-"reading" time:

The stretch of time during which a test subject can continue to receive toxicant from its surroundings, from its food, from its own surface, or however, is termed the exposure time. The time passing between the start of application or administration of a toxicant and the moment when the result of the test is "read" or determined in terms of the response of the test subject is the reaction time. This latter becomes important when a subject is exposed to a toxicant for a given period then removed to a place where there is no further exposure to additional toxicant, but where the subject may be held for some additional time before the response is determined, or the results of the test read. If the test involves study of the effects of contact of the subject with a residual deposit, then exposure time and inspection time are the same, if contact of subject and toxicant is maintained until response determination. Sufficient prolongation of exposure time or reaction time will yield, eventually, a maximum effect for the dosage received. Speed of action is the inverse of the time needed for the effect of a particular dose to reach its maximum. It is not the time needed for a particular dose to yield a stated response.

The action of a toxicant may be weighed from the standpoint of its power to yield a certain effect on the test subject, such as producing immobility, excitement, death, etc., regardless of time taken to produce the effect. Determining a toxicant's action from this standpoint sets aside variables such as speed of action or uptake. On the other hand, the determination of a poison's action may be made in full consideration of action speed or uptake speed. Each type of assessment of toxicant action carries its own special conditions. In the first case highest, maximum, or end-point effects must be determined, and thus exposure time and reaction time must be sufficiently long to yield the end-point. However, if this length of time is so great as to permit starvation, adventitious changes, or to outrun the normal longevity of the subject, plainly, other assessments of action are needed. However, the results obtained by the first type of determination or assessment are those more generally meaningful and valid. Results based on reaction and exposure times of an intermediate duration are set by the action speed. In case of residual films results may be affected or changed by influences which alter speed of uptake from the film or speed of reaction to the amount of toxicant taken. To gain the fullest knowledge of toxic action and data sufficient for valid comparisons, studies should be made to yield time-mortality data for various dosages of toxicant as well as data for dosages applied in terms of set exposure or reaction periods.

VII) Temperature and toxic action; humidity and toxic action:

Tabular and other materials indicating the nature and extent of temperature effect on insecticide toxic action are included in section 173. At this point a few remarks may serve to generalize those data. Temperature effect on the action of insecticides on insect test subjects is particularly marked when studied in terms of the temperature at which the test insects are held after treatment. These effects, have shown up, particularly when studied after administration of toxicants by mouth and by direct contact with the insect body, in the form of differences in toxicity of the toxicant and in the time needed to yield one or another form of response. In the case of many poisons higher holding temperatures after treatment with toxicant yield higher mortalities—within physiological limits, of course. Although some data are offered in section 173, less is known about the influence of environmental temperature in the pre-treatment period. Variation in the size of the temperature coefficient depends on many things—the toxicant itself, the specific nature of the test subject, the conditions of the test, and the physical state in which the toxicant is administered. Whether the temperature coefficient is positive or negative depends, apparently most usually, on the insecticide itself, although conditions of test and type and state of test subject no doubt have some influence. Different environmental temperatures for the treated insects, then, yield differences in relative and absolute toxicity of a toxicant, considered alone and in combination with other toxicants or with various forms of the one poison. DDT and some of its close relatives are notable in showing a negative temperature coefficient, in terms of post-treatment temperature, for a number of commonly used test insects. But this effect is by no means common to all the so-called chlorinated hydrocarbons. Temperature during the course of treatment also influences the rate of response to a toxicant. If, however, an insect is treated with a toxicant at a given temperature and held at the same temperature during the post-treatment period the effect is not essentially different when that given temperature obtains only during the post-treatment period.

Humidity of the insect environment before treatment with a toxicant—provided humidity is not such as to affect adversely the vitality or physiological condition of an insect—seems to play no part in affecting the toxicity of a substance. Humidity has been said to influence the toxicity of residual deposits during the exposure period but studies of this effect of humidity are few, incomplete, and not particularly ingenious. Far more is known about the very real effects and problems of humidity on the phytotoxicity of insecticides.

VIII) Other factors:

The amount of toxicant absorbed by some mosquitoes and the housefly, exposed in a space misted with kerosene solutions of pyrethrins, has been shown to be related to the movement activity of these flying insects. Active flying movement apparently increased the dosage of toxicant received upon the body. It is also reported that movement of actively crawling insects enhanced the toxicity of insecticidal deposits. The self-grooming activities of cockroaches and flies which have been dusted, or have picked up insecticidal dusts from dusted environments, have been shown to enhance the mortality by adding a gastrointestinal intoxication to the contact toxicity. Obviously, this would be true in the case of a toxicant relatively low in toxic effect by contact, but good in stomach poisoning power. Most insects, at least as adults, groom themselves and those doing so most persistently and actively might be expected to show the foregoing effect more than others. Effects have been described in toxicity tests of insecticides as due to intensity of light, palatability, repellent nature of insecticide or formulation, anaesthesia, intestinal motility or intestinal stasis, aeration (in fumigant insecticide tests), admixture of carbon dioxide with certain fumigant vapors and impurities in the toxicants used.

In these prefatory remarks many useful indications have not been touched on at all. The author again wishes to draw the attention of the reader to those sections of the text which deal with certain general aspects of insecticides and their action or with natural chemical "families" of insecticides. A number of such sections treat of quite new agencies as yet scarcely explored, for example, section 6 on antibiotic and antimetabolite effects in insects. The general problem of the hazard of insecticides for useful and beneficial insects—for bees, for pollinators, for insects parasitic on noxious species—is approached operationally through tabulations of known data in section 12. Although this section deals chiefly with bees, many of these observations have general validity beyond the immediate horizon of the apiculturist.

With respect to toxic effects of insecticides applied on a grand scale, few good critical studies have been made. In section 183 on Toxaphene®, however, there has been set down a *precis* of some excellent field experiential data gathered from happenings in several southern cotton-growing counties where insecticides distributed on a grand scale, combined with certain circumstances of weather, yielded very drastic effects on wildlife. Such a study, though limited, serves as a working model and a guide.

Certain sections in the text may seem odd, for example, section 44 on the effect of insecticides on cytochrome oxidase. Why single out this enzyme and devote to it a section, however brief? Simply because these data presented as a coordinated unit were gathered by one investigator on a sizeable number of different insecticides and lent itself to such unique presentation. The vastly richer documentation on the effect of certain insecticides on choline esterase is not so treated and a reader of the text may be baffled by an apparent major omission. However, reflection will suggest that it is primarily the organic phosphate insecticides and the carbamates and carbamic acid esters which inhibit the biochemical action of the esterases for acetylcholine and its chemical relatives. Thus, it is in the general sections, namely sections 27 and 134, that the nature and meaning of this enzyme inhibition by insecticides is explored. Again, why section 145 on phytotoxicity which deals with a handful of species of garden shrubs and trees? The same reasons obtain as those offered for the section on cytochrome oxidase—a coordinated block of comparable data given by one assiduous worker on purely horticultural woody plants. Elsewhere, under the sections given over to specific insecticides, abundant phytotoxicity data may be found.

The best way to learn the uses of this work, if the author may so suggest, is a careful perusal of the subject index to appraise the general range of its subject matter. Then, a consideration of a few of the insecticides—such as DDT, Parathion, Pyrethrins, Rotenone, for which there are varied and abundant data—will give a good idea of the general internal arrangement and method of presentation of data followed throughout. Not all the same headings appear in every section. Plainly, an insecticide used solely to control body lice or a substance to repel chiggers from the human body present little scope for any data on phytotoxicity; no such section may be expected to appear even if only to report the absence of specific data.

Hindsight sees deficiencies which even the most earnest application and arduous thought while work was in progress did not bring to notice. For these deficiencies there is real regret; but there is hope that sufficient usefulness, if not excellence, is at hand so that readers will be moved to suggest corrections for deficiencies, omissions, and sins of commission. If the work has value and is found to deserve at some future time to be reissued in expanded and ameliorated form to keep it abreast of a burgeoning subject, then the deficiencies of the present may be changed into the virtues of the future.

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