PESTICIDE FORMULATIONS

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PREFACE

The cost of discovering and developing a new pesticide runs between five and ten million dollars. The time lag between discovery and marketing averages 77 months: 7430 compounds are screened for every marketable toxicant. The number of man years of effort to clear a new pesticide for the U.S. market averages 65.* Economic and manpower commitments of this magnitude have required that increased attention be directed towards greater understanding of all aspects of pesticidal formulations.

This is not a "how to" formulations recipe book. Rather, its objectives are to foster a greater understanding of fundamental principles involved in research on pesticidal formulations.

Once a candidate pesticide is mixed with anything (a slurry of the compound in water qualifies) the composition may be considered a pesticidal formulation. Hence, any research on a combination of an active compound and a second material is research on a pesticidal formulation. Any instance where the added material will affect the chemical, physical, and biological properties of an active biocide is fair game for this book.

Let us briefly survey some of the principles touched upon in this volume. The biological activity of a compound can be mathematically correlated with experimentally determined physical properties of that compound. Two parameters which correlate very well are (1) a solubility coefficient denoting the ability of a compound to move to an active site and (2) the Hammett sigma constant of one or more substituents which can be related to the reactivity of a compound at the active site. An inert ingredient is capable of changing the apparent solubility coefficient of the toxicant. Hence it is logical that the current new technology on biological correlations be presented as a first chapter in this book.

A few additional principles emphasized in the following chapters include (1) the importance of solubility relationships as indicated by the HLB system in selecting an emulsifier, (2) the effect of the phase inversion temperature on emulsion stability, (3) the dehydrating effect of fertilizer salts on emulsifiers and the resultant stability or instability of the emulsion,

*Chemical Week, July 26, 1972, page 18.

(4) the catalytic effect of clays and other carriers on the degradation of a pesticide, (5) the all-important flowability property of a mixture as it relates to the successful manufacture of a dry pesticidal formulation, and (6) the physical properties of formulations and how they affect the size of the particles in a spray and the movement of the particles in air.

The physical properties of a formulation and its resultant spray solution as indicated by particle size and surface properties (surface tension, contact angles, spreading coefficient) will dictate whether or not a spray droplet will adhere to a plant surface. Once a pesticide is on a target site it is faced with a lipid barrier which must be penetrated to affect biological activity. An understanding of the physical and chemical properties of this barrier can aid the formulator in designing his composition for optimum penetration and efficacy. And finally, when the formulation finds its way to the soil, the adsorption characteristics of the ingredients of the composition on soil colloids will dictate how far the pesticide will move with possible concomitant danger of contamination of soils and ground waters far removed from the site of application.

It is obvious that one should not routinely add inerts to pesticides just to get the right handling properties. One must consider the effect of the additives on the biological activity of the toxicant, on processing, and on the movement on or in the host and its environment. Through a better understanding of all the principles involved, one hopes that the formulator will be able to optimize his formulations in terms of efficacy and reduction of deleterious side effects.

The scope of this book is very broad, as is the whole subject of the evaluation of pesticidal formulations. It could not have been written without the expert cooperation of all the contributors to this volume. They are all recognized experts in their fields and I express my sincere gratitude to them all for participating in this endeavor.

St. Paul, Minnesota
October, 1972

Wade Van Valkenburg

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Chapter 1

CORRELATION OF BIOLOGICAL ACTIVITY WITH CHEMICAL STRUCTURE AND PHYSICAL PROPERTIES

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I. INTRODUCTION

Throughout the course of the past century and particularly during the last two decades, we have witnessed a remarkable "chemical revolution" by which man has achieved a great measure of success in the development and utilization of synthetic organic chemicals. Although these have been, and continue to be, of great benefit to almost all aspects of modern life, there is little doubt that the most remarkable advances have been made in the chemical control of those organisms which are either directly or indirectly opposed to man's well-being. Thus the widespread use of a vast number of synthetic agricultural chemicals which include insecticides, herbicides, fungicides, and veterinary drugs has dramatically increased both the quality and quantity of the food and fiber derived from our crops and domestic animals. Similarly our suffering has been greatly alleviated and life expectancy enhanced by the successful development of drugs to control diseases associated with pathogenic organisms and of chemical correctives to counterbalance our natural deficiencies. Because the one common property of all these chemicals resides in their ability to interact with living systems they can all be said to possess some form of biological activity. The fact that many are biocidal indicates that this activity has lethal consequences to some forms of life.

The first organic materials employed by man for various medicinal and agricultural purposes were generally of natural origin and unknown structure. As the chemical nature of the active components of these materials was recognized and the compounds themselves were isolated, characterized, and subsequently synthesized in pure form, considerable interest was shown in possible relationships which might exist between their chemical structure and biological effect. Interest in this area has continued to increase and today investigations involving the correlation of chemical structure with biological activity have far-reaching ramifications in many different fields. For the chemist and biochemist such studies may serve to provide information on possible reaction mechanisms or on the structural nature of the biochemical receptor sites involved in certain processes. For the toxicologist they can often afford an important method of studying the mode of action of toxic agents. Perhaps most important of all, correlation studies have considerable practical application in providing some rationale to aid the designer of new and potentially more effective drugs and agricultural chemicals.

The reader is referred to the following books, reviews, and discussions all of which excellently cover many aspects of this vast field of interest (1-5). Although these are largely concerned with medicinal and pharmaceutical chemistry, all cover important principles of general relevance to any consideration of materials possessing biological activity.

This chapter constitutes a discussion of some of the major factors involved in considerations of structure-activity relationships and of mathematical approaches which attempt to express these factors in quantitative terms. Although the examples given to illustrate specific points will be taken largely from the field of agricultural chemistry and will mainly involve chemicals of a toxic nature, it should not be construed that the importance of structure-activity relationships is limited to those chemicals which interfere with normal living systems. On the contrary, it should be emphasized that the normal functioning of any living organism depends on a multiplicity of highly specific, highly organized relationships between the structure and biological activity of its naturally occurring chemical components.

II. BIOLOGICAL ACTIVITY

A. General

All living organisms are chemically dynamic systems; they behave and function as living entities as a direct result of an amazing complexity of interdependent chemical reactions which although in continuous flux are maintained at any given time in a delicate state of balance. The presence of a "foreign" chemical within a living system can readily upset this balance by enhancing, inhibiting, or otherwise interacting with one or more of the chemical reactions or components on which its integrity depends. Such a chemical can be said to possess some form of biological activity.

Biological activity can take many different forms and may be measured in different ways depending on the level at which the investigation is conducted. When the critical site and mechanism of action of a chemical are known, biological activity can be measured directly in terms, for example, of the degree of inhibition or enhancement of an enzyme system as measured in vitro. More usually, however, biological activity is measured in an indirect manner through in vivo observations of the end result of the chain of events initiated by the interaction of the chemical with some unknown biochemical component. In the case of a pesticide, for instance, it is customary to measure biological activity in terms of the per cent mortality of an organism without necessarily having any knowledge of the mode of action of the material at the molecular level. More strictly defined this should be termed biological effect or response. The observable in vivo response to some biologically active chemical is often difficult to relate to the critical disturbance at the molecular level from which it results. Thus in the case of a mammal poisoned with an organophosphorus insecticide one would not readily connect death through respiratory failure, the

observable biological effect, with the inhibition of cholinesterase which constitutes the true biological activity of this particular group of compounds.

B. Factors Determining Biological Effect

Studies involving the correlation of biological activity with chemical structure are extremely complex and until recently have been based almost entirely on empirical observations of a qualitative or semi-quantitative nature. This results largely from the complex series of events which can take place between the initial application of a material to an organism and its arrival at, and subsequent interaction with, a biological receptor (Fig. 1). These factors which effectively compete with the receptor for the chemical include: failure to penetrate and translocate to the site of action, storage in inert tissues, and degradative metabolism and excretion. The relative importance of any one factor depends on the physical and chemical characteristics of the material in question. A chemical, therefore, must not only possess the correct structure to interact with a specific receptor, but must also incorporate structural features which will allow it to successfully circumnavigate these competing factors, each of which constitutes a potential barrier to prevent the material from reaching its site of action. As a result, the interpretation of data obtained in structure-activity investigations usually increases in complexity as the level of the investigation moves from the true in vitro system to that existing in the intact organism.

When structure-activity investigations are carried out in vitro, the material of some specific tissue or organ is homogenized and the enzyme or other cell component under investigation is isolated and perhaps purified to some extent. Under these relatively uncomplicated conditions the chemical under consideration can be placed effectively in direct contact with the target or receptor site, and the results usually serve as a good qualitative indicator of the absolute structural features required to effect a specific type of biological activity. In view of the high degree of complementary character which must exist between a chemical and its biological receptor, it is likely that structure-activity relationships determined in vitro will truly reflect the structure of the receptor surface. Consequently a great deal of our present knowledge regarding the three-dimensional structure of biological receptors has been obtained from in vitro studies on the structural nature of the chemicals with which they interact.

The in vitro activity of any chemical depends primarily on steric factors such as size, shape, and stereochemical configuration. It is these properties which determine the relative position of specific substituent groups

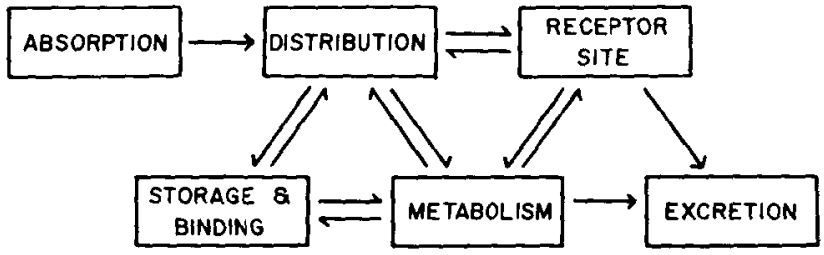

FIG. 1. The interactions of a chemical between its initial application and its reaction with a target receptor.

through which binding and/or chemical reaction with the receptor takes place. The actual types of interactions between chemicals and cellular components are many and varied, ranging from the largely irreversible formation of covalent bonds to rather loose, usually reversible complexes resulting from hydrogen bond formation, ionic and dipole interaction, van der Waals forces, or hydrophobic bonding. Most of these interactions are effective over only relatively short intermolecular distances so that optimal biological activity is obtained only if the molecular size and stereochemical configuration of the chemical allows it to come into close juxtaposition with the relevant receptor surface.

Although still considered to be at the in vitro level, the results of studies involving the use of intact isolated cells in the form of either tissue slices or discrete organs become increasingly more difficult to evaluate. In this case the chemical must not only possess the properties previously discussed in relation to its activity at the receptor surface but, in addition, must incorporate properties which allow it to traverse one or more of the lipophilic membranes or ion impermeable barriers which will otherwise prevent it from reaching its site of action. Under these conditions it is fairly obvious that the physical properties of the chemical can have a marked quantitative effect on its biological activity even if the material possesses the necessary structural requirements to interact at the molecular level. As we shall see such properties as lipid/water partition coefficients and ionic dissociation often play a dominant role in determining biological activity.

In the intact living organism a chemical must meet still further structural criteria before it is able to elicit a biological response. First it must be capable of reaching its site of action which may be far removed from its point of application to the organism. This involves penetration through such tissue as mammalian skin, the highly lipophilic epicuticular layer of insect cuticle, the polysaccharide phosphoprotein materials of bacterial membranes, or the outer cuticle and cellulose cell walls of

plant tissues. Having achieved the penetration of this outer protective sheath the material must move relatively freely through a number of lipoprotein cell membranes to some site where it must seek out and interact with a specific receptor. During this translocation process the chemical is often exposed to the action of strong acids, as in the mammalian gastric juices, or to alkalis, as in the gut contents of many lepidopterous larvae. It must in addition be capable of withstanding the potentially degradative action of a multiplicity of enzyme systems and must avoid being effectively removed from the system through binding with the large variety of inert proteinaceous and lipophilic materials with which it comes into contact.

For these reasons considerable caution should always be exercised in attempts to predict the probable in vivo effect of a material based solely on information regarding its in vitro performance. Often a chemical which demonstrates a high degree of biological activity in vitro proves to be entirely inactive when applied to the intact organism. Alternatively metabolic alteration of the chemical in vivo may produce a compound of much greater activity than would be suggested by the in vitro activity of the parent compound. The insecticide parathion is inactive as an inhibitor of cholinesterase in vitro; however, it is extremely toxic to many forms of life as a result of its oxidative conversion in vivo to the potent anticholinesterase paraoxon.

In summary therefore the biological activity of any material is governed by several major factors which include its ability to successfully penetrate the organism and to subsequently translocate to its site of action, its ability to avoid binding and storage in inert components and tissues, its ability to withstand the action of degradative enzymes, and ultimately of course, its ability to interact with some essential biological receptor. The extent to which a chemical satisfies any of these requirements is a function of its chemical structure and physical properties.

III. ABSORPTION AND DISTRIBUTION

A. General

In order to exert its biological effect a chemical must be capable of penetrating the several barriers frequently interposed between its point of application to the organism and its biochemical receptor site. When a drug or pesticide has the necessary structural characteristics for biological activity in vitro, its failure to initiate a response in the intact organism often results from the fact that the material docs not possess the necessary physico-chemical properties which allow it to cross one or