DRUG DESIGN

Edited by E. J. Ariëns

VOLUME IX

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DEPARTMENT OF PHARMACOLOGY
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Preface

The positive response to Volumes I–VIII of *Drug Design* and the rapid developments in this field warrant continuation of this series.

Chapter 1 of Volume IX elucidates efforts to avoid toxicity, not only of drugs, pesticides, and food additives but also of chemicals in general. Various aspects of the development of bioactive agents, including the optimalization of existing agents by the development of more efficient prodrugs, e.g., transport forms, and of special delivery forms are presented in Chapters 3 and 5 respectively.

More theoretical approaches to drug design also receive attention: Hansch's paradigm is applied to industrial practice in Chapter 2, multivariate statistics is applied to pharmacochemistry in Chapter 4, and computer-assisted drug design is described in Chapter 7. Chapter 6 presents a new and promising approach to the study of spatial arrangements in bioactive molecules that is especially important in the analysis of structure–activity relationships. The aim of the authors has been to present the reader with insight into both promising and actual developments in the field of drug design. The topics are presented in an informative, concise, systematic, and thought-provoking manner, in which speculations and new perspectives are encouraged.

The presentations in Volumes I–VIII as well as those in Volume IX indicate the wide scope of *Drug Design*. It is hoped that the reader will find the interdisciplinary approach fruitful.

E. J. Ariëns

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Chapter 1 Design of Safer Chemicals

E. J. Ariëns

I. Introduction

In the past the primary concern of both the chemical industry and the individual chemist was the economical production of agents that served a particular purpose in an optimal way. This resulted in a wealth of chemical products (e.g., plastics, insecticides, weedkillers, food additives, drugs, and dyes) touching practically every aspect of life. After the fulfilment of the primary objectives, and with a growing awareness of the hitherto often unrecognized or neglected risks inherent in chemical

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agents, the emphasis is more and more on safety. Since the Softenon disaster in 1961, this has become clearly manifest for drugs and food additives. The recognition and reevaluation of the impact of pesticides on ecological systems has resulted in a more critical approach in that field. The detection of long-term risks, such as carcinogenesis and mutagenesis caused by, for example, monomers in plastic manufacturing, has resulted in legislation with regard to protection against chemical health risks in general. TOSCA, the Toxic Substances Control Act, introduced recently in the United States, is an example of things to come.

For new chemicals, whatever purpose they may serve, the balance between advantages and disadvantages, among which health risks will be highly significant, will have to be assessed before acceptance for application. The goals are not to cure but to prevent, implying efforts to design safer chemicals. The term "design" indicates that the new agents will be developed on as rational a basis as possible, reducing the trial-and-error factor to a minimum and thereby avoiding situations where major or minor disasters are needed to point up the problem. Design involves control of potentially toxic actions of chemical agents by molecular manipulation, which requires an insight into the chemical mechanisms of toxic action, and therewith an insight into the relationship between structure and toxic action.

II. Toxic Action

A complex sequence of processes constitutes the basis for toxic action. It can, however, be split up in three main phases (Fig. 1) (*5*).

1. The exposure phase. This is composed of the factors or processes that are risk-determining in the handling of or exposure to potentially toxic substances. The most toxic agents, i.e., agents that are toxic at extremely low dosages, are by no means the most dangerous ones. The risks as a rule are mainly determined by the chance of contact with the toxon, the method of contact (i.e., the type of han-

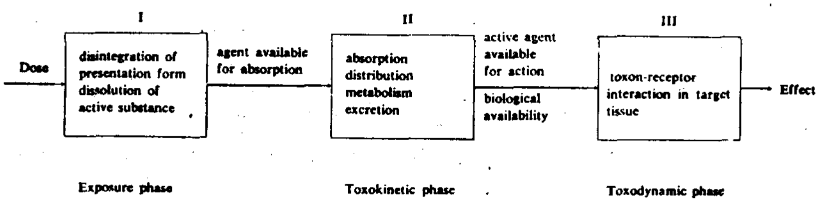


Fig. 1. Schematic representation of the main phases of toxic action.

dling), and thus the extent of absorption. The degree or efficacy of exposure as a function of time, the "exposure profile" is a determining factor. These profiles depend on, for instance, the presentation form of the toxon, the formulation, the concentration, the route of exposure (skin, oral, etc.), and the time course of exposure.

2. The toxokinetic phase. This involves those processes involved in absorption, distribution, excretion, and metabolic conversion of the active agent. The fraction of the dose that reaches the general circulation is a measure of the biological or systemic availability. The plasma concentration as a function of the time provides the "biological availability profile." The concentration of the toxon in the target tissue, related to the time, gives the "physiological availability profile."
3. The toxodynamic phase. This covers the processes involved in the interaction of the toxic agent and its molecular sites of action (receptors). This interaction results in the induction of a stimulus that initiates a sequence of biochemical and biophysical events finally leading to the effect. The characteristics of the toxodynamic phase form the basis for the toxicological classification of agents.

Various aspects of the main phases of toxic action, especially with regard to the molecular mechanisms, will be discussed as a basis for the design of safer agents, which will then be exemplified.

III. The Exposure Phase

Preventive factors in this phase are the proper labeling and instruction for the use of potentially toxic agents and the use of safe containers for handling. An example of the latter is the "child-resistant" packaging (*77*) not only of drugs but of household chemicals. With regard to industrial hygiene, it should be emphasized that giving the less intelligent or less educated worker the dirty, often risky, work indicates a lack of either social conscience or intelligence on the part of those in charge. An understanding by those exposed of the risks involved is a prerequisite to safe handling.

The uptake of a chemical by the organism is highly dependent on both the degree and the rate at which the substance in an absorbable (as a rule the molecularly dispersed) form comes into contact with an absorbing surface of the organism. In case of occupational poisoning as well as air pollution, the respiratory system is the primary route. In occupational poisoning, the skin is also an important path. Oral ingestion is practically restricted to toxon residues in food and to accidental poisoning.

The particle size, the relative lipid–water solubility, and the metabolic stability are determinant factors for both the persistence or the accumulation in the environment and in biological systems. For instance, the half-life in soil of the insecticide diflubenzuron is ½–1 week for a particle size of 2 microns and 8–16 weeks for a particle size of 19 microns (*71*).

Lipid solubility is an important factor for possible penetration through intact skin. Hydrophilic agents such as strongly ionized molecules can barely pass. This holds true for biological membranes (usually composite membranes, such as the intestinal epithelium) in general. Physiological conditions also play a role. For penetration through the skin, humidity of the skin, temperature, and the type of contact (e.g., via clothing soaked with the agent) influence absorption (Fig. 2) (*28*). For retention in case of

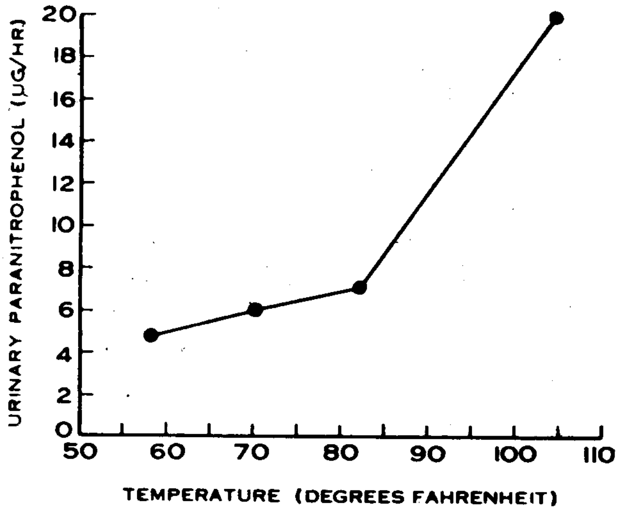


Fig. 2. The average hourly rates at which *p*-nitrophenol was excreted in urine for 41 hours following dermal exposure at different temperatures to 5 grams of a 2% parathion dust by three volunteers (Funckes, *28*).

inhalation, particle size and respiratory depth and volume per unit of time—which in their turn are dependent on, e.g., physical exertion, humidity, and temperature—play a role.

Control of toxicity or enhanced selectivity in action can be obtained by molecular manipulation. In the synthesis of dyes, mainly azo dyes, organic amines are important intermediates. These amines penetrate the skin readily and are potentially toxic; an example is β-naphthylamine which is a strong carcinogen. The extreme dangers associated with the handling of such substances could be brought under control by alteration

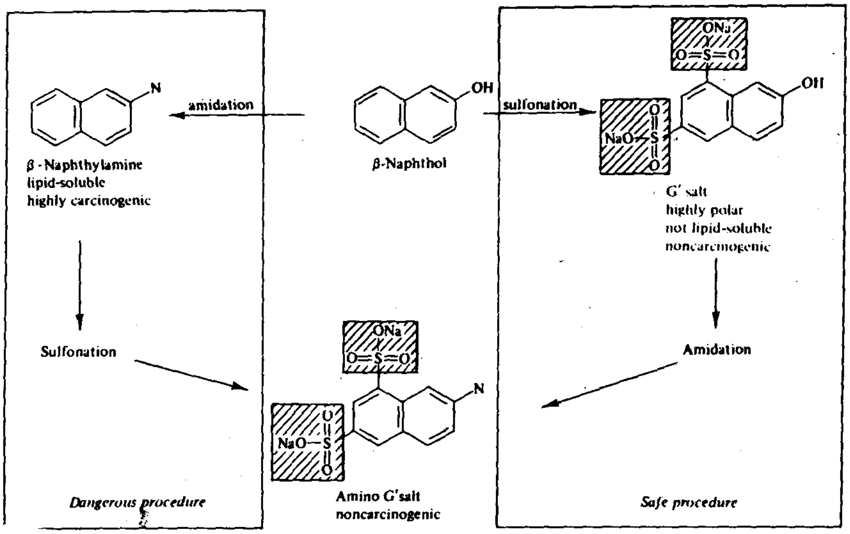
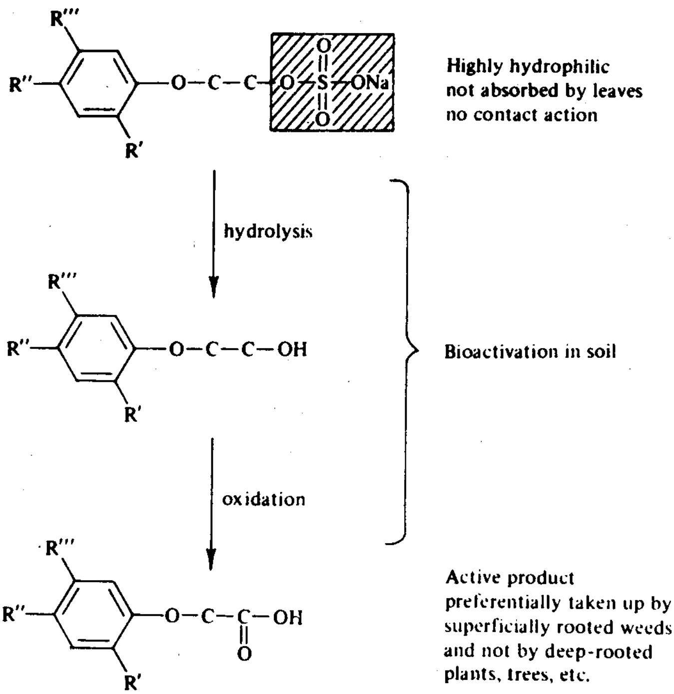


Fig. 3. Safeguarding of an industrial chemical process by adaptation of the route of synthesis, namely early introduction of toxicity-reducing distribution-restricting moieties (after Scott, *75*).

of the synthetic pathway. As shown in Fig. 3, introduction early in the synthetic procedure of the highly hydrophilic sulfonic acid groups, necessary in the final product anyway, produces a safe procedure by avoiding the potentially toxic lipophilic aromatic amines (*75*). Control of absorption by introduction of highly ionized groups is also realized in the development of selectivity in action, and thus reduction in adverse effects, of weedkillers (Fig. 4) (Crafts, 1957) (*18*). Plants with extensive foliage are exceptionally vulnerable to lipid-soluble weedkillers. Because of the large surface and the waxy character of that surface, hydrophilic compounds cannot penetrate. Such compounds can, however, be taken up by plant roots. Superficially rooting plants will be more vulnerable than deep rooted plants, trees, etc., as a result of the dilution and degradation involved in the process of penetration to deeper soil layers. Besides making use of high polarity, therewith restricting lipid solubility and thus absorption, as discussed before, there is the possibility of making use of polymeric agents which, due to their size, are not taken up by the biological systems and which are therefore restricted in their distribution (*27*). This approach holds true for chemicals in general, such as pigments, additives to plastics, and preservatives for wood. As far as protection against insects is concerned, the latter may be made digestible for insects, so that the toxon is liberated and a target-directed systemic action is



R'	R''	R'''	
—C	—Cl	—H	Methin
—Cl	—Cl	—H	Sesin
—Cl	—Cl	—Cl	Natrin

Fig. 4. Selectivity in action of weedkillers obtained by introduction of highly hydrophilic, disposable restricting moieties in a precursor compound (after Crafts, *18*).

obtained. This insolubilization approach also holds true for food additives such as colorants and even sweeteners. The fact that certain bioactive agents, e.g., insulin, remain bioactive after irreversible binding to a polymeric carrier such as sephadex and the fact that proteins such as monellin and thaumatin, which have such a molecular size that they cannot penetrate cells, have an intensely sweet taste, indicate that as long as the sites of action for such agents are located on the cell surface, this approach may be feasible. In this respect, polymers with chelating qualities may also be mentioned; such polymers are suitable, for instance, for extraction of metals from the effluent of sewage clearing plants and are even to be used as oral antidotes in the case of metal poisoning. The use of insoluble polymers will facilitate both recovery and recycling and will restrict dissipation in the environment. A disadvantage might be no or poor biodegradability.

IV. The Toxokinetic Phase

The main aspects of this phase are the transport, especially via lipid membranes (involved in absorption, distribution, and excretion), and the metabolic conversion of the chemical agent.

A. MODULATION OF TRANSPORT

Passive transport via biological membranes is strongly dependent on relative lipid–water solubility and therewith on the partition coefficient of the agent. Introduction of strongly hydrophilic groups will restrict not only absorption, but also cell penetration; the compound, as far as absorbed, tends to stay in the extracellular fluid where it is readily available for excretion in the urine, for which hydrophilicity is advantageous.

Figure 5 shows how introduction of a quaternary onium group in an organic phosphate (irreversible acetylcholinesterase inhibitor) restricts the distribution of the agent to the extracellular compartment (*59*). For insecticidal action, lipophilicity is a requirement, since otherwise the compound will not be absorbed sufficiently. In clinical use, cell penetration, and particularly penetration of the blood–brain barrier with concomitant interference with central nervous system action, is to be avoided. The quaternary derivatives thus find application in the therapeutic treatment of glaucoma.

The use of azo dyes as food colorants has had serious consequences. The azo dye butter yellow, used to give winter butter the appearance of spring and summer butter, is for instance, a strongly carcinogenic agent. It is now substituted by lipid-soluble carotinoids. The incorporation of highly hydrophilic sulfonic acid groups into the azo dyes provides agents that are hardly if at all absorbed from the intestinal tract and which, when absorbed, are limited in their distribution mainly to the extracellular fluid and which are readily excreted in the urine. A characteristic of the azo and many other types of food colorants accepted for usance by the WHO (*89*), is the presence of such highly ionized groups. Since the intestinal flora are capable of reducing the azo link, one must be sure that each of the moieties in the molecule linked by azo groups has been safeguarded by sulfonic acid groups (Fig. 6) (*4*).

A counterpart to the poor absorption and rapid elimination of strongly

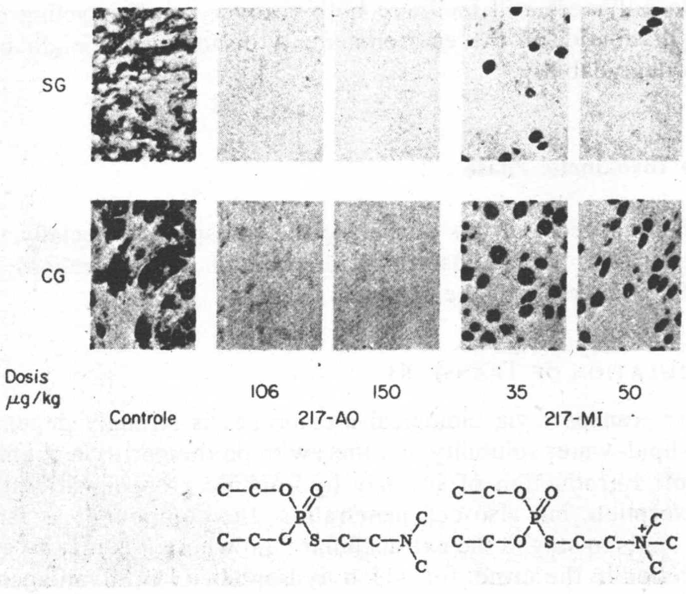


Fig. 5. The distribution of two organophosphates, a lipid-soluble tertiary base (217-AO) and a hydrophilic quaternary ammonium compound (217-MI) in the ganglion stellatum (SG) and ganglion ciliare (CG) of the cat. Note: the esterase activity (dark areas) is blocked intra- and extracellularly by the lipid-soluble compound and only in the extracellular space by the quaternary ammonium compound (McIsaac *et al.*, *59*).

hydrophilic agents is the easy absorption and accumulation tendency in the biological organisms of highly lipophilic, metabolically stable agents, of which DDT is an example. This compound and its also strongly lipophilic and metabolically stable dehydrochlorination product DDE show a high accumulation factor in biological organisms and an extremely long half-life (*64*) (Fig. 7), with as a result a strong accumulation along food chains (*19*) (Fig. 8).

Another example of lipid solubility and metabolic stability resulting in persistence and accumulation is that of the plasticizers abundantly present in a variety of plastic containers, among which are the disposable plastic blood-transfusion sets. Plasticizers are mostly phthalic acid esters; one of the best known is diethylphthalate (DEHP), which is resistant to the various body esterases. This highly lipophilic agent migrates not only to lipid food stuffs (Table I) (*84*) but also to the blood, when blood comes into contact with plastics rich in plasticizers (Fig. 9) (*46*). This results in a persistent accumulation of DEHP in the tissues of patients after blood

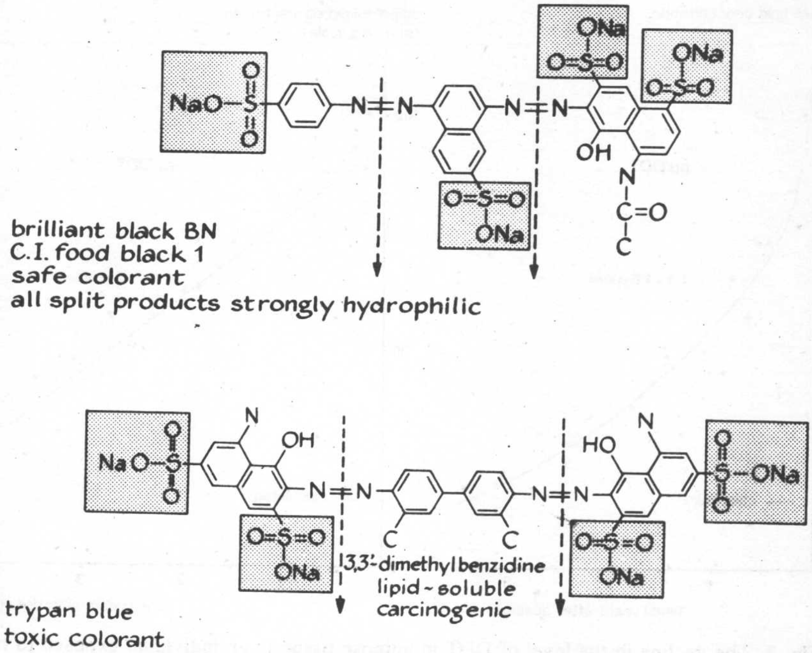


Fig. 6. Two azo dyes bearing strongly ionized sulfonic acid groups. If used as food colorant, one must take the azo reduction (arrows) by intestinal microorganisms into account. In case of trypan blue, the reduction results in the formation of a lipid-soluble carcinogenic benzidine derivative. In brilliant black, correctly, all three moieties linked by azo groups are safeguarded by strongly ionized groups reducing toxicological risks.

transfusions. In experiments with monkeys, a persistence of up to 14 months in liver and adipose tissue is observed (*3*, *45*, *46*).

In the cases of both the insecticide DDT and the plasticizer DEHP, one might consider the development of more hydrophilic agents. The possibilities in this respect are, however, very restricted since the absorption of the contact insecticide by the insect as well as the incorporation of the plasticizer into the plastics require a relatively high lipid solubility. The solution to this problem has been found in a reduction of metabolic stability, and it will be discussed in the section on modulation of metabolic conversions (IV,B).

An intermediate position, as far as lipid–water solubility coefficients are concerned, is taken by weak organic acids and bases. Such agents are, in the ionized form, restricted in membrane penetration and thus in both initial biological absorption and reabsorption in the kidney; they do pass freely in the nonionized form. This means that the pH in the environment