INTERNATIONAL ENCYCLOPEDIA
OF PHARMACOLOGY & THERAPEUTICS
Section 113

Differential Toxicities of Insecticides and Halogenated Aromatics

Editor:
F. MATSUMURA

PERGAMON PRESS

INTERNATIONAL ENCYCLOPEDIA OF
PHARMACOLOGY AND THERAPEUTICS

Section 113

DIFFERENTIAL TOXICITIES OF INSECTICIDES AND HALOGENATED AROMATICS

SECTION EDITOR

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PERGAMON PRESS

OXFORD · NEW YORK · TORONTO · SYDNEY · PARIS · FRANKFURT

U.K. Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England

U.S.A. Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.

CANADA Pergamon Press Canada Ltd., Suite 104, 150 Consumers Rd., Willowdale, Ontario M2J 1P9, Canada

AUSTRALIA Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, N.S.W. 2011, Australia

FRANCE Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France

FEDERAL REPUBLIC OF GERMANY Pergamon Press GmbH, Hammerweg 6, D-6242 Kronberg-Taunus, Federal Republic of Germany

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First edition 1984

Library of Congress Cataloging in Publication Data
Main entry under title:
Differential toxicities of insecticides and halogenated aromatics.
(International encyclopedia of pharmacology and therapeutics; section 113)
'Published as Supplement No. 13 (1983) to the review journal Pharmacology & therapeutics.'—Verso t.p.
Includes index.
1. Insecticides—Toxicology—Addresses, essays, lectures.
2. Insecticides—Metabolism—Addresses, essays, lectures.
3. Aromatic compounds—Toxicology—Addresses, essays, lectures.
4. Organohalogen compounds—Toxicology—Addresses, essays, lectures.
I. Matsumura, Fumio. II. Series.
RA1270.I5D54 1983 615.9'02 83-4113

British Library Cataloguing in Publication Data
Differential toxicities of insecticides and halogenated aromatics.—(International encyclopedia of pharmacology and therapeutics; section 113)
1. Insecticides—Toxicology
I. Matsumura, Fumio II. Series
632'.51 RA1270.I5

ISBN 0-08-029826-5

Published as Supplement No. 13 (1983) to the review journal *Pharmacology & Therapeutics.*

Printed in Great Britain by A. Wheaton & Co. Ltd., Exeter

INTERNATIONAL ENCYCLOPEDIA OF
PHARMACOLOGY AND THERAPEUTICS

Executive Editor: A. C. SARTORELLI, *New Haven*

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PREFACE

PESTICIDES are biocidal agents which are intentionally used on biological systems. Insecticides constitute the most toxic group of chemicals to animals. As a result, their use must be carefully regulated and their actions must be understood as far as possible.

It is well known that studies on the mechanisms of action of insecticides have led to many important pharmacological and biochemical discoveries. Good examples are those on nicotine, fluoroacetic acid, rotenone, organophosphates, and carbamates.

The relationship between pesticides and halogenated aromatics has been largely historical. However, there are a number of reasons why these chemicals are studied together. Halogenated aromatics have physicochemical properties similar to those of chlorinated hydrocarbon pesticides. Moreover, some of them have been used as pesticides and others have been found in pesticidal preparations. For instance, pentachlorophenol (PCP) has been used as a pesticide. Among its residues hexachlorodibenzo-*p*-dioxin was found to cause toxic symptoms in chicken (i.e. 'chick edema' factor). PCB residues were originally found among environmental samples as a result of efforts to distinguish DDT metabolites from other contaminating materials. The search for the toxic, teratogenic and acnegenic contaminant of 2,4,5-T, a hormone-type herbicide, has led scientists to discover TCDD and so on. From the viewpoint of action mechanisms of these chemicals, many common features have been found.

The toxic manifestation of any of these chemicals in animals is a result of a complex series of interactions between the chemical and its metabolites and various biological systems within the animal. Factors affecting toxicities are exposure, uptake, metabolism, distribution, excretion, target interactions, etc. The theme of this book is differential toxicity, i.e. how toxic expressions are affected by these factors. Toxicity in this book refers to all deleterious actions recognizable in animals, not just acute lethality. It is rare that one has the opportunity to summarize the colossal amounts of information pertinent to the toxic actions of an important group of chemicals, with the unified goal of explaining processes leading to differential toxicity. Certainly the key is timing, and I believe that the time is right, with so many interesting key discoveries in this field in the last decade and the scarcity of books and reviews covering the entire subject area.

In preparing this book each author has been carefully selected from among recognized experts. Each author was asked to summarize the significant events in the field and to come up with perspectives and with the necessary details to accomplish the task. The intended readership is expert scientists, including fellow toxicologists who may wish to use this book as a reference source, and advanced graduate students who plan to specialize in this area.

The editing task was made pleasant by the helpful collaboration offered by Dr A. C. Sartorelli and Dr Barbara Z. Renkin, of the Department of Pharmacology, Yale University School of Medicine, and editors of *Pharmacology & Therapeutics*, and by the able assistance of Miss Karen Smith and Mrs Alice Ellis at the Pesticide Research Center, Michigan State University.

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CHAPTER 1

EXPOSURE TO INSECTICIDES

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1. INTRODUCTION

The subject of 'pesticide exposure' is not a well defined one. The problem is that there are many different ways by which humans can be exposed to pesticides and there may be many reasons why such exposures do take place. In general, the probability of exposure increases with the frequency of handling of pesticides. Also, as more people have the chance to handle pesticides, the more likely that accidental exposure can occur. Moreover, social, economic, cultural, psychological and other factors play roles in determining the rate and frequency of pesticide exposure in man. Here, for the sake of clarity, we have limited the scope of this review to the actual physical occurrence of exposure and to the methods to analyze the problem. In treating the subject matter we have grouped the cases of exposure into two classes, cases of direct and indirect exposures, since these two types of exposure require very different approaches for study.

The overall purpose of this review is to give an overview of the subject matter of exposure as related to safety against pesticides. Thus, many toxicological aspects of exposure studies have been omitted from the review. There have been several review papers and book chapters covering certain areas of this subject. Hayes (1975) wrote an excellent book on the overall subject of toxicology with abundant references to safety. Various medical aspects and occupational safety are covered. Brooks (1976) summarized the knowledge on 'penetration and distribution of insecticides'. A more recent publication discussing the implications of occupational exposure to pesticides was by Gunther and Gunther (1980).

2. TOXICITY OF PESTICIDES AS AFFECTED BY ADMINISTRATION ROUTE

Pesticides are biologically active compounds intended mainly to kill pest populations by their toxic or other deleterious reactions. They are thus one of the most regulated groups of chemicals in many societies. Toxicity data are usually expressed in terms of their LD_{50} or ED_{50} (effective dose) values. Depending upon the duration of exposure to bring about the toxic reaction, toxicity dosages are frequently expressed as acute, sub-acute or chronic doses. Here the nature of the compound is the most important factor to consider. Some compounds may be toxic in acute tests, but not in chronic tests and vice versa.

It is known that the toxicity of pesticides is manifested most quickly via intravenous injection, since such a method introduces pesticides into the blood system in a most direct manner. By the same line of reasoning, the speed of action of pesticides depends upon the speed with which the compound reaches the blood system. Exposure to pesticides through the lung (i.e. inhalation) is a dangerous route, since pesticides which come in through the alveolar system get into the blood system quickly.

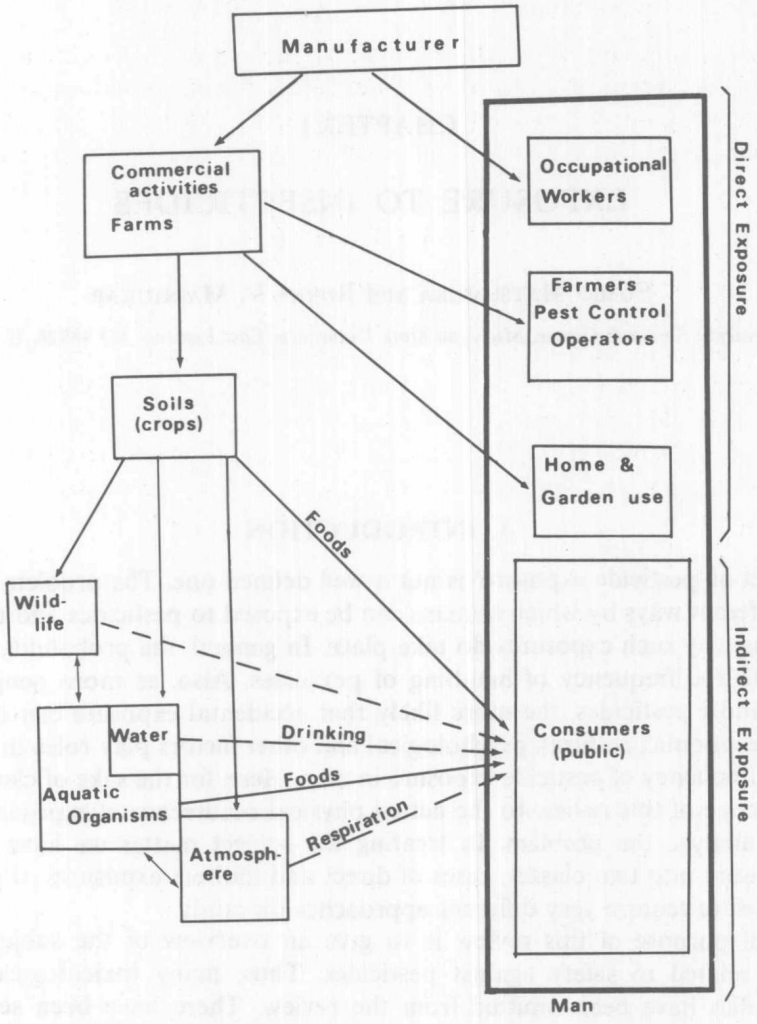

FIG. 1. Schematic representation of exposure of man to pesticides.

3. GENERAL PATTERNS OF EXPOSURE

In Fig. 1 we have summarized the ways by which man can have exposure to pesticides. The scheme also shows how pesticides are gradually diluted and spread in the environment. In brief there are two ways the general public can be exposed to pesticides. The first way is by using pesticides for homes and gardens, and the second through residues in foods, drinking water and the air. In the former case the method of protection must come from regulatory efforts by governments such as labeling, pesticide use education, and mechanical inaccessibility (such as special push-twist caps to prevent children from touching). On the other hand, in the latter case, governments' actions on tolerance of pesticide residues in food commodities are necessary.

Direct exposure involves people who actually handle insecticides, such as occupational workers of the pesticide manufacturing industry, formulators and professional spraymen. This type of exposure also extends to people who are users of pesticides, such as farmers and home gardeners, as well as persons who either accidentally or intentionally come into contact with pesticides. Indirect exposure to pesticides comes mainly from residues in food and in the environment in general, and usually involves a larger segment of the population than in cases of direct exposure. The distinction between these two types of exposure is that in the former case the persons are aware of the possibility of exposure and can identify the source, whereas in the latter case the people have no direct knowledge of the presence and the source of the contaminant.

4. DIRECT EXPOSURE TO PESTICIDES

For any toxic compound to reach the target organs to exert its action, it must first enter into the body system through some route. Under normal conditions the three most important natural routes for gaining entry are (1) oral (gastrointestinal), (2) respiratory, and (3) dermal routes, though occasionally other routes such as the eye may also be involved.

4.1. Oral Exposure

Oral exposure to pesticides, strictly speaking, has not been a major problem as an occupational hazard except for cases of inadvertent ingestion. However, occasional cases of poisoning related to suicidal or homocidal intent have been reported from time to time. Apart from the practical considerations, this route of exposure to pesticides is important for toxicological reasons; evaluation of the toxicity of any compound is based mainly on a comparison of the oral LD_{50} values (Table 1). All other evaluations concerning the mode of action and biochemical lesions produced by pesticides are also usually done after administration of the test compound orally. Exposure by this route attracts a more practical consideration, as discussed later, when the exposure is through residues of pesticides in food, where the amount of the residue ingested is small but exposure continues for longer periods of time.

When pesticides are ingested, they are first transported to the upper and then to the lower gastric tracts. From there penetration of one or more membranes should be achieved in order for them to enter the blood system. Lipid-solubility of the compound seems to play some role in influencing the absorption of pesticides by this route. The intestinal mucosa of mammals engulfs droplets of fat that may be seen in the cytoplasm, from where they make their way into the lymphatic vessels. Imai and Coulston (1967) showed the presence of electron-dense particles associated with fat-droplets following large doses of methoxychlor ingestion probably representing a complex associated with the compound. Thus it is possible that for lipophilic compounds lipid-mediated transport is the major mode of penetration through the intestinal wall. On the other hand, some nonionized and ionized lipid-soluble compounds are known to be absorbed by the stomach. For instance, some highly ionized materials such as paraquat and diquat are also known to be absorbed by this route, presumably by forming complexes with phospholipid peptides, analogous to the case of quaternary nitrogen drugs. There is some evidence that sparsely soluble materials, either in lipids or water, have problems in penetrating the intestinal wall. For instance, most of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) and OCDD (octachlorodibenzo-*p*-dioxin), orally given with corn oil, are excreted in feces unabsorbed (Piper *et al.*, 1973; Norback *et al.*, 1975). Whenever there is some difficulty in gastric absorption of any pesticidal chemicals, the percentages of absorption become less as the total quantity of pesticides increase. Thus in the case of dieldrin oral poisoning of rats, the amount of dieldrin excreted into feces (i.e. unabsorbed by digestive systems) is significant at high doses and only on the first day of ingestion (Matthews *et al.*, 1971).

4.1.1. *Oral Exposure among Occupational Workers*

As mentioned above, oral exposure does not really pose a problem among occupational workers, regardless of the compound or nature of the work involved. However, the most commonly occurring oral poisoning is, for example, ingestion of contaminants with foods. That is, in spite of the warnings against smoking and eating during work, exposure by this route does occur sometimes. For instance Quinby *et al.* (1963) report a case of serious poisoning of parathion in which the worker had carried a partially opened candy bar in his pocket while spraying. The hands are frequent carriers of pesticides. For instance, Armstrong *et al.* (1973) found, on an average, 0.002 mg or more of parathion on that portion of the sandwiches which workmen held in their hands while eating the other half.

TABLE 1. *Acute Oral and Dermal Toxicity of Insecticides to Male Rats* (data taken from Gaines* (1960, 1969)

Compound	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)
Chlorinated hydrocarbon insecticides		
Aldrin	39	98
Chlordane	335	840
DDT (Tech.)	217	2510 (F)
Dieldrin	46	90
Dilan	>3000	6900
Endosulfan	43	130
Endrin	17.8	18
Heptachlor	100	195
Isodrin	15.1	35
Kelthane	1100	1230
Kepone	125	>2000
Lindane	88	1000
Mirex	740	>2000
Perthane	>4000	—
Toxaphene	90	1075
Organophosphorus insecticides		
Abate	8600	>4000
Chlortion	880	1500–4500
DDVP	80	107
Diazinon	108	900
Dipterex	630	>2000
EPN	36	230
Guthion	13	220
Fenitrothion	740	300–400 (estimated)
Fensulfothion	4.1	19
Dursban	155	202
Malathion	1375	>4444
Naled	250	800
Methyl Parathion	14	67
Parathion	13	21
Phosdrin	6.1	4.7
Phosphamidon	24	143
Ronnel	1250	1000–2000 (Rb)
Ruelene	4	2000–4000 (Rb)
Schradan	9.1	15
Thimet	2.3	6.2
Toichloronate	55	180
Propoxur	83	>2000
Aminocarb	30	275†
Mexacarbate	37	1500–2500 (estimated)†
Carbaryl	850	>4000
Aldicarb	0.8	3

*Except in the cases mentioned F = female rat, Rb = Rabbit.

†Values are from Kenega and End (1974).

Exposure to pesticides through smoking of contaminated cigarettes has been neglected by occupational workers. In such instances workers carry cigarettes in their shirt or overall pockets and handle them without washing the contaminated hands. In a recent study on the exposure of workers to parathion through cigarettes Wolfe *et al.* (1975a) found that the greatest contamination occurred through unwashed hands. Contamination of emulsifiable concentrate thus imparted was 235.6 μg per cigarette. These authors calculated that, if a worker smokes twenty contaminated cigarettes in a day, he would theoretically be taking in 4.7 mg of parathion per day. This amount is more than the 3 mg per day level that could be absorbed without decreasing the cholinesterase level. However, during normal spray operations the potential of exposure through cigarettes is not particularly high. For instance measurement of endrin in cigarettes handled by

spraymen showed a maximum of only 0.002 mg of endrin per cigarette (Wolfe *et al.*, 1963).

4.1.2. *Exposure to General Public*

Apart from the hazard of occupational exposure, direct oral exposure is more important in cases of accidental poisoning and in fatal poisonings resulting in suicide or homicide through ingestion of massive doses. The number of incidences of accidental poisonings increases as the number of people who handle the pesticide increases. Thus pesticides used in homes and gardens become significant sources of accidents. For example the US Department of Agriculture (USDA, 1977) studied the cases of common household cockroach baits with kepone and found in such cases that low toxicity and selectivity (i.e. low mammalian toxicity) are not always a guarantee of the safety of the pesticide. Of fifty-six incidents reported, fifty-two of them occurred with children under five years of age; two incidents involved adults and the other two involved unspecified ages. All but nine of the young children were exposed primarily to control devices for ants and cockroaches. The fact that the highest number of children's accidental poisonings by chemicals has been recorded with aspirin clearly indicates this tendency. Another source of oral exposure is pesticides accidentally mixed in foods. The most frequently occurring cases are those involving the pesticide-treated seeds. For instance, the use of hexachlorobenzene-treated seed grains for food in Turkey in 1959 resulted in over 3,000 cases of serious poisoning.

4.2. Respiratory Exposure

Respiratory exposure to pesticides merits important consideration in industrial toxicology, as it is often the main natural route of exposure in manufacturing and formulating insecticide plants. This route is also an important portal of exposure to insecticides among the general public due to the presence of the residues in the community air. In general, the most crucial factor in determining the importance of an inhalation route is the chemical nature and the mode of availability, such as mist spraying, vaporizer application, etc., of the pesticide involved. With volatile chemicals such as fumigant insecticides, the probability of respiratory poisoning easily increases.

4.2.1. *Absorption Through the Respiratory Route*

Respiratory absorption of chemicals tends to be more rapid than absorption through other portals because of the abundant blood supply and the thinness of the alveolar membrane. For pesticides to come in through this route, however, they must be in the form of gas, vapor or fine particles. Solid and liquid particles are applied as dusts, sprays, mists, fogs and aerosols, where the particle size ranges from 0.4 μm (fine aerosols) to 750 μm (spray) (Potts, 1958). A few of the fumigant pesticides are gases; others are liquids which rapidly vaporize. Structurally the respiratory tract is such that particles (1–30 μm in size) inhaled through the nose are able to settle on the bronchial walls. The lining of the nasopharynx and the tracheobronchial tree is ciliated, facilitating the passage of inhaled particles into the pharynx and respiratory tree. The aerodynamics of the respiratory tract are also such that the velocity of the airflow gradually decreases from the nasopharyngeal region and is almost zero in the alveoli. These features of the respiratory tract result in particles of size 1–30 μm being trapped and finally deposited in the lung. Smaller particles, especially those less than 0.1 μm, are less likely to be deposited in the lungs. Though the rate of absorption by this route of only a very few pesticides has been

measured, it is generally assumed that the bulk of pesticides entering the lung are absorbed. LaBelle and Brieger (1959) studied the clearance of particulate material deposited on the lungs in rats and observed that it is cleared, at least partially, in two phases. The time of clearance is also proportional to the size of the particle. Clearance is accompanied by an increase in the free-moving phagocytotic cells in the lung and is facilitated by the ciliary action on the particles in the nasopharynx (LaBelle *et al.*, 1960). Insoluble particles are cleared more slowly through the process of lymphatic uptake and solubilization (Casarett, 1972).

4.2.2. *Measurement of Respiratory Exposure*

In industry, measurement of the concentration of a chemical in the ambient air is a common practice, on the assumption that this represents the concentration of the chemical being inhaled by the worker. This method holds good for toxicants which are in the form of gas, vapor, or very fine particles but may not be valid for toxicants in the form of larger particles or when their concentration in the air changes from time to time. One important point to remember in air sampling is to obtain particles of the size that are picked up by the nostrils in breathing, by imitating the aerodynamics of human respiration (American Conference of Government and Industrial Hygienists, 1972). It is also important to select a suitable solvent to use in impingers or absorbents. Ethylene glycol was found to be a valuable medium for collecting parathion (Miles, 1965). Another way of collecting samples of toxicants in air is to use some kind of filter instead of solvent. If it is desirable to collect particulate materials of the environment, a convenient method may be to use collecting screens (Blifford *et al.*, 1965). Nylon chiffon fabric pretreated with 10 per cent ethylene glycol in acetone was observed to be a suitable screen. Trapping the toxicant directly in the air inhaled by the person exposed to it is a more valuable method. There is a relatively new method of toxicant analysis whereby pesticides in breath are examined by high sensitivity gas chromatography and infrared spectroscopy (Stewart, 1974).

4.2.3. *Respiratory Exposure to Pesticides among Occupational Workers*

Wolfe *et al.* (1967) extensively reviewed the extent of respiratory and dermal exposure of workers to pesticides. They found that in the case of factory workers, respiratory exposure is much less, amounting to only 0.75 per cent of the total dermal plus respiratory exposures. Several factors, such as the type of formulation, concentration, method of application etc., influence the rates of exposure. These factors play an important role in determining the extent of respiratory exposure among workers involved in spraying pesticide formulations. Based on their study, Wolfe *et al.* (1967) found that respiratory exposure was highest for aerosols, intermediate for dusts and low for dilute spray formulations. Thus, the smaller the particle size, the higher the proportion of the total dispersed material that can be expected to be inhaled. Several other factors such as the state of the formulation of the spray and the object the spraystream strikes, also play a significant role on the extent of exposure by this route.

In determining the toxicological significance of exposure by any particular route, the actual amount of the pesticide that a worker is exposed to is even more important. Thus in many cases the duration of exposure becomes an important factor to consider. Durham and Wolfe (1962) attempted to extrapolate the LD_{50} values of rats for men depending upon the dosage received by exposure in one hour. Wolfe *et al.* (1967) noted that in a large number of studies carried out, only three compounds, endrin, parathion and tepp, were used in such a way that the percentage of toxic dose that is absorbed per hour exceeds 1 per cent. Thus if the workers are limited to contact with pesticide for only a few hours a day, they would not receive a large enough amount to be poisoned.

In many cases it is hard to distinguish whether exposure occurred by way of respiratory or dermal routes. Most occupational exposures, however, tend to be considered

dermal because of the wide area of the exposed skin. Respiratory exposure could be more prominent among fumigation workers and among aircraft sprayers. In an experimental study Oudbier *et al.* (1974) attempted to evaluate the actual hazard of pesticide exposure via the respiratory route, in several kinds of occupational operations and farming activities. These authors observed that the pesticide mixing and tank filling operation-period presents a high potential risk of respiratory exposure. Wolfe *et al.* (1975b) studied the exposure of workers engaged in apple thinning operations to parathion residues by dermal and respiratory routes. These investigators noted that the highest exposure through inhalation occurred at the 1-hr post-treatment period (0.15 mg/hr) and continued at 0.03 mg/hr at 96 hr. They concluded that an apple thinning operation following parathion treatment poses a potential exposure to this pesticide only when all the measurable parathion for dermal and respiratory exposures is completely absorbed.

As explained before, respiratory exposure to pesticides could also occur by smoking contaminated cigarettes during handling operations, though generally this route of exposure does not seem to be considered as a serious hazard by the worker (Wolfe *et al.*, 1975a). However, such a level of exposure may, when added to the already higher than normal exposure through the dermal route, become a significant factor.

The importance of the respiratory route, as compared to the dermal route, also varies with the environment in which the pesticides are used. For instance, in the case of DDT spraying, Wolfe *et al.* (1959) demonstrated that the extent of pesticide intake by workers through the former route was 3.4 mg/kg while that through the latter route was 1755 mg/kg (i.e. 0.19 per cent of the total dose was through the respiratory route). In the case of the outdoor spray, on the other hand, the corresponding figures were 0.11 mg/hr and 243 mg/hr, making the percentage of respiratory exposure 0.045 per cent.

Various spraying operations often give high levels of exposure to man. According to Wassermann *et al.* (1960), as much as 3 mg/hr of BHC is taken in by workers during forest spraying, and during an air blast spraying in fruit orchards, workers received 0.54 mg/hr of azinphosmethyl (Wassermann *et al.*, 1963).

Hand operated sprayers tend to increase the risk of respiratory exposure. In the case of parathion spraying, as much as 0.19 mg/hr in fruit orchards (Batchelor and Walker, 1954) to 0.29 mg/hr in tomato fields (Simpson and Beck, 1965) are taken up via this route, while corresponding figures for air blast spraying operations usually range in the order of 0.06 mg/hr (Batchelor and Walker, 1954).

Less toxic insecticides such as carbaryl and malathion are usually handled with few protective measures. Comer *et al.* (1975) studied the potential dermal and respiratory exposure of formulating plant workers and spraymen to carbaryl. Among formulating plant workers, potential respiratory exposure to carbaryl was 1.1 mg/hr, while for spraymen it was 0.09 mg/hr. The combined mean dermal and respiratory exposure for formulating plant workers was only 0.03 per cent of the percent toxic dose per hour and 0.02 per cent for spraymen, although at this level acute toxic effects would be minimal.

Copplestone *et al.* (1976) investigated the extent of exposure of spraymen in Sudan to dimethoate, an organophosphorus insecticide. The results of the analysis of the respirator pads showed a maximum exposure of 19.9 μg per day which, together with dermal exposure, was 0.053 per cent of the toxic dose potentially received per day. This level of exposure is far below the estimated 1 per cent of the toxic dose per hour necessary to exert toxic effects.

4.3. Dermal Exposure to Pesticides

The importance of exposure to pesticides by this route has not received enough attention, presumably because the older poisons are poorly absorbed through skin. Today there is no question about the importance of dermal exposure, because many of the modern pesticides are effectively absorbed by skin, and the vast majority of industrial poisonings are through dermal and/or respiratory exposure.