

**THE WORKER HAZARD POSED BY REENTRY INTO PESTICIDE-TREATED
FOLIAGE: DEVELOPMENT OF SAFE REENTRY TIMES, WITH EMPHASIS ON
CHLORTHIOPHOS AND CARBOSULFAN**

(In: The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case
Studies, D.J. Paustenbach, Editor, John Wiley and Sons, Inc. New York, NY)

HS-970

JB Knaak², Y Iwata³ and KT Maddy¹

California Department of Food and Agriculture
Division of Pest Management, Environmental Monitoring
and Worker Safety
Worker Health and Safety Branch
1220 N Street
Sacramento, California 95814

California Department of Health Services²
Sacramento, California

ICI Americas Inc.
Richmond, California

RA 427.3
R57

AUG 21 1989 *mt/Reg*
State of California #5757/5756
Department of Food & Agriculture
Pest Management Division
1220 N Street
Sacramento, California 95814
P.O. No. 9001-703

The Risk Assessment of Environmental and Human Health Hazards: A Textbook of Case Studies

Edited by

DENNIS J. PAUSTENBACH

ChemRisk™ Division, McLaren Environmental Engineering, Alameda, California



WILEY

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS

New York · Chichester · Brisbane · Toronto · Singapore

The Worker Hazard Posed by Re-entry into Pesticide-Treated Foliage: Development of Safe Reentry Times, with Emphasis on Chlorthiophos and Carbosulfan

J. B. Knaak

California Department of Health Services, Sacramento, California

Yutaka Iwata

ICI Americas Inc., Richmond, California

K. T. Maddy

California Department of Food and Agriculture, Sacramento, California

1 INTRODUCTION

The introduction of organic pesticides into modern agriculture has increased production and provided consumers worldwide with high-quality fruits and vegetables. The continuous use of these materials, however, has resulted in contamination of water, soil, and air. The chlorinated hydrocarbons, principally DDT, were the first class of compounds to be recognized as toxic environmental pollutants. DDT was replaced in the 1950s by an ever-growing number of biodegradable but dermally toxic organophosphorus and *N*-methylcarbamate insecticides. The use of these pesticides, principally ethyl parathion, on citrus in California resulted in a series of serious poisoning incidents among workers reentering treated groves to harvest fruit.

Established preharvest intervals (time between the last application of pesticide) varying from several days to several weeks were originally considered to be adequate to protect the health of workers "entering" or "reentering" a sprayed crop to harvest fruit or vegetables. Workers entering treated crops for activities other than harvesting (e.g., thinning, pruning) were not protected by the preharvest interval. On an annual basis in California there are over 300,000 field workers involved in handling crops treated at sometime with

TABLE 1. Chemical Identification of Pesticides Mentioned in Text

| Pesticide | Chemical Designation |
|-----------------|---|
| Acephate | <i>O, S</i> -Dimethyl acetylphosphoramidothioate |
| Aldicarb | 2-Methyl-2(methylthio) propionaldehyde <i>O</i> -(methyl carbamoyl) oxime |
| Azinphosmethyl | <i>O, O</i> -Dimethyl <i>S</i> -(4-oxo-1, 2, 3-benzotriazin-3(4 <i>H</i>)-yl) methyl phosphorodithioate |
| Carbaryl | 1-Naphthyl methylcarbamate |
| Carbofuran | 2, 3-Dihydro-2, 2-dimethyl-7-benzofuranyl methylcarbamate |
| Carbosulfan | 2, 3-Dihydro-2, 2-dimethyl-7-benzofuranyl-[(di- <i>n</i> -butylamino)thio] methylcarbamate |
| Chlorobenzilate | Ethyl-4, 4'-dichlorobenzilate |
| Chlorthiophos | <i>O</i> -[2, 5-Dichloro-4(methylthio)phenyl] <i>O, O</i> -diethyl phosphorothioate |
| Dialifor | <i>S</i> -[2-Chloro-1-(1, 3-dihydro-1, 3-dioxo-2 <i>H</i> -isoindol-2-yl)ethyl] <i>O, O</i> -diethyl phosphorodithioate |
| Dimethoate | <i>O, O</i> -Dimethyl <i>S</i> -(<i>N</i> -methyl carbamoylmethyl) phosphorodithioate |
| Dioxathion | <i>S, S'</i> -(1, 4-dioxane-2, 3-diyl) bis(<i>O, O</i> -diethyl phosphorodithioate) |
| Ethion | <i>O, O, O', O'</i> -Tetraethyl <i>S, S</i> -methylene diphosphorodithioate |
| Malathion | <i>O, O</i> -Dimethyl <i>S</i> -[1, 2-di(ethoxycarbonyl) ethyl] phosphorodithioate |
| Methamidophos | <i>O, S</i> -Dimethyl phosphoramidothioate |
| Methidathion | <i>S</i> -[(5-Methoxy-2-oxo-1, 3, 4-thiadiazol-3(2 <i>H</i>)-yl)methyl] <i>O, O</i> -dimethyl phosphorodithioate |
| Methomyl | <i>S</i> -Methyl- <i>N</i> -[(methylcarbamoyl)oxy] thioacetimidate |
| Mevinphos | 2-Methoxycarbonyl-1-methylvinyl dimethyl phosphate |
| Monocrotophos | Dimethyl 1-methyl-2-(methylcarbamoyl) vinyl phosphate |
| Oxamyl | <i>S</i> -Methyl <i>N, N'</i> -dimethyl- <i>N</i> -[(methylcarbamoyl)oxy-1-thiooxamimidate] |
| Paraoxon | <i>O, O</i> -Diethyl <i>O</i> -(4-nitrophenyl) phosphate |
| Parathion | <i>O, O</i> -Diethyl <i>O</i> -(4-nitrophenyl) phosphorodithioate |
| Phosphamidon | 2-Chloro-2-diethylcarbamoyl-1-methyl vinyl dimethyl phosphate |
| Thiodicarb | Dimethyl <i>N, N'</i> [thio-bis(methylimino) carbamoyloxy thioacetimidate] |

pesticide chemicals. The large number of workers, crops (e.g., 692,000 acres of grapes, 175,000 acres of citrus), and organophosphorus and *N*-methylcarbamate pesticides used (< 1,500,000 lb annually) on foliage on these two crops provide an insight into the potential magnitude of the field reentry problem as it exists in California alone.

This chapter presents poisoning cases reported in California agriculture, field management of these poisoning cases, federal and state regulatory responses, and the development of research procedures for characterizing dislodgeable foliar residues, their transfer to skin and clothing, their percutaneous absorption, and their effect on red cell cholinesterase activity. Currently acceptable procedures for calculating "safe foliar residues" and "safe reentry intervals" based on reentry research are provided using a number of pesticides employed in agriculture. Chemical designations of pesticides mentioned in the text are listed in Table 1.

2 HISTORICAL BACKGROUND

2.1 Poisoning Incidents

Poisoning incidences among workers who reentered pesticide-treated groves and vineyards were first reported in California in 1949 after the registration of ethyl parathion,

TABLE 2. Incidence of Multiple Case Systemic Illnesses of Agricultural Field Workers from Exposure to Residues of Organophosphorus Pesticides in California, 1949-1986

| Date | Location | Number 111 | Probable Number Exposed | Crop and Activity ^a | Parathion | Pesticides Implicated | ALA ^b | Worker Entry Time ^c | Previous Applications of Other Organophosphates the Same Season | |
|--------|------------|---------------|-------------------------------|-----------------------------------|-----------|--------------------------|------------------|--------------------------------------|---|-----------------------|
| | | | | | | | | | Pesticide Used | Interval ^d |
| 7/8/49 | Marysville | 20-25 | 56 | Pears | Parathion | | 2.50 | 12 | | |

TABLE 2. Incidence of Multiple Case Systemic Illnesses of Agricultural Field Workers from Exposure to Residues of Organophosphorus Pesticides in California, 1949-1986

| Date | Location | Number Ill | Probable Number Exposed | Crop and Activity ^a | Pesticides Implicated | AIA ^b | Worker Entry Time ^c | Previous Applications of Other Organophosphates the Same Season | |
|------------|--------------|------------|-------------------------|--------------------------------|---------------------------|------------------|--------------------------------|---|-----------------------|
| | | | | | | | | Pesticide Used | Interval ^d |
| 7/8/49 | Marysville | 20-25 | 56 | Pears | Parathion | 2.50 | 12 | — | — |
| 6/27/51 | Delano | 16 | 24 | Grapes | Parathion | 1.87 | 33 | — | — |
| 8/27/52 | Riverside | 11 | 30 | Oranges | Parathion | 2.00 | 16 | — | 19 |
| 7/6/53 | Riverside | 7 | — | Oranges | Parathion | — | 17 | — | — |
| 7/ /53 | Riverside | — | — | Citrus | Parathion | — | 34 | — | — |
| 7/ /53 | Bryn Mawr | — | — | Citrus | Parathion | — | 33 | — | — |
| 7 /59 | Entire state | 275 | — | Citrus | Parathion | — | — | — | — |
| 10/5/61 | Terra Bella | 10 | — | Lemons | Parathion | 3.00 | 17 | Parathion | 97 |
| 8/9/63 | Hughson | 94 | — | Peaches | Parathion | 2.00 | 14-38 | Parathion | 36-110 |
| 6/29/66 | Terra Bella | 9 | 15 | Oranges | Parathion | 1.87 | 15 | — | — |
| 7/8/66 | Porterville | 6 | 11 | Oranges | Parathion | 1.33 | 32 | — | — |
| 7/21/66 | Lindsay | 3 | 30 | Oranges | Parathion | 2.00 | 13 | — | — |
| 8/2/66 | Navalencia | 11 | 22 | Oranges | Parathion and malathion | 13.50 | 28 | — | — |
| 8/11/66 | Terra Bella | 9 | 28 | Oranges | Parathion and ethion | 3.75 | 28 | — | — |
| 9/2-23/67 | Hughson | 23 | — | Peaches | Azinphosmethyl and ethion | — | 46 | — | — |
| 9/17-18/67 | Ballico | 3 | — | Peaches | Azinphosmethyl | 1.50 | 30 + | TEPP | 15 30 |
| 5/ /68 | Lindsay | 19 | — | Oranges | Parathion | 200 | 38-47 | — | — |
| 5/5/70 | Porterville | 3 | 30 | Lemons, pruning | Azinphosmethyl | 1.75 | 66 | None | None |
| 5/25/70 | Lindsay | 2 | 22 | Oranges | Dioxathion and ethion | 3.75 | 38-47 | — | — |
| 5/27-28/70 | Terra Bella | 8-11 | — | Oranges | Parathion and ethion | 600 | 1 | — | — |
| | | | | | Parathion and ethion | 1.00 | 1 | — | — |
| | | | | | Azinphosmethyl and ethion | 7.50 | 14 | Parathion | 17 |
| | | | | | Azinphosmethyl and ethion | 6.75 | 14 | — | — |
| | | | | | Azinphosmethyl and ethion | 12.00 | 8 | Azinphosmethyl | 10-12 |
| | | | | | | 4.00 | 11 | — | — |

TABLE 2 (Continued)

| Date | Location | Number Ill | Probable Number Exposed | Crop and Activity ^a | Pesticides Implicated | AIA ^b | Worker Entry Time ^c | Previous Applications of Other Organophosphates the Same Season | |
|------------|-----------------------|---------------|-------------------------------|-----------------------------------|-------------------------------|------------------|--------------------------------------|---|-----------------------|
| | | | | | | | | Pesticide Used | Interval ^d |
| 9/14-17/70 | McFarland | 35 | 35 | Oranges | Parathion | 9.00 | 34-37 | Dioxathion | 120 |
| 10/1/70 | Orosi | 11 | 55 | Oranges | Parathion and malathion | 3.00 | 31 | Azinphosmethyl | 180 |
| 8/16-24/71 | Orange Cove | 8 | 9 | Olives, pruning | Parathion | 6.00 | 31 | — | — |
| 5/6/72 | Lind Cove | 3 | — | Oranges | Parathion | 2.50 | 21 | — | — |
| 9/15/72 | Exeter | 9 | 22 | Oranges | Parathion | 5.00 | 12 | — | — |
| 9/9/72 | Huron | 4 | 31 | Lettuce, weeding | Parathion | 2.50 | 1 | Parathion | 4-25 |
| 8/30/73 | Fowler | 27 | 32 | Grapes | Dialifor | 1.00 | 39 | Phosalone Phosmel | 41 57 |
| 9/3/74 | Kerman | 2 | 5 | Grapes | Azinphosmethyl | 1.00 | 28 | Ethion | 57 |
| 6/12/75 | Lemon Cove | 16 | 20 | Oranges | Parathion | 2.00 | 16-20 | Phosalone | 67-68 |
| 6/76 | Fresno | 4 | 4 | Lettuce, thinning | Mevinphos | — | 14 h | None | None |
| 9/8-10/76 | Madera | 118 | 120 | Grapes | Dialifor | 1.00 | 10 | Phosalone | 93 |
| 7/16/77 | Orange Cove | 39 | 39 | Oranges | Parathion | 5.00 | 22 | — | — |
| 6/10/78 | Tulare | 7 | — | Grapes | Ethion | — | 16 | — | — |
| 8/14-15/80 | Ballico | 6 | 24 | Peaches | Azinphosmethyl | 1.50 | 32+ | Phosalone | — |
| 7/11/80 | Salinas | 22 | 22 | Cauliflower, banding | Mevinphos and phosphamidon | 1.00 | 3 h | — | — |
| 4/23/81 | King City | 41 | 80 | Lettuce | Mevinphos | 1.00 | 2 h | — | — |
| 8/3/82 | Strathmore | 17 | 32 | Oranges | Parathion | 7.50 | 35 | Parathion | — |
| 9/18/82 | Salinas | 35 | 35 | Cauliflower, banding | Mevinphos | 1.00 | 1 | Oxydemeton-methyl | 1 |
| 4/16/82 | Salinas | 17 | 27 | Cauliflower, weeding | Oxydemeton-methyl | 0.50 | 1 | Dimethoate | 1 |
| 6/17/83 | San Juan, Burrleta | 2 | 2 | Irrigating | Azinphosmethyl | — | <1 | — | — |

| | | | | | | | | | |
|---------|-----------------------|----|-----|--|------------------------------|--------------|------|-------------------|---|
| 4/23/81 | King City | 41 | 80 | Lettuce | Mevinphos | 1.00 | 2 h | — | — |
| 8/3/82 | Strathmore | 17 | 32 | Oranges | Parathion | 7.50 | 35 | Parathion | — |
| 9/18/82 | Salinas | 35 | 35 | Cauliflower, banding | Mevinphos | 1.00 | 1 | Oxydemeton-methyl | 1 |
| 4/16/82 | Salinas | 17 | 27 | Cauliflower, weeding | Oxydemeton-methyl | 0.50 | 1 | Dimethoate | 1 |
| 6/17/83 | San Juan, Bautista | 2 | 2 | Irrigating | Azinphosmethyl | — | <1 | — | — |
| 5/22/84 | Firebaugh | 2 | 2 | Cotton, irrigating | Chlorpyrifos and acephate | 1.00 0.75 | 6 h | — | — |
| 7/15/85 | Ducor | 4 | 15 | Grapefruit | Parathion | 8.00 | 48 | — | — |
| 6/13/86 | Watsonville | 2 | 9 | Strawberries, weeding | Malathion | 2.00 | 21 h | — | — |
| 7/2/86 | Five Points | 25 | 32 | Cotton, weeding | Methamidophos | 0.50 | 2 h | — | — |
| 7/31/86 | Three Rocks | 3 | 40+ | Cotton, running from border patrol | Methamidophos | 0.80 | 1 h | — | — |

*Unless otherwise indicated in Crop column, workers are engaged in picking operation.

^bActive ingredient expressed in pounds per acre.

^cDays postapplication (unless otherwise stated).

^dDays elapsed between exposure date and the most recent previous application.

^eDash means unknown.

Source: California Department of Food and Agriculture.

as shown in Table 2. The poisonings were characterized by sweating, vomiting, dizziness, and general body weakness. Red blood cell cholinesterase was depressed in most cases more than 20%. This and the poisoning incidents described later indicated to state and federal regulatory officials that "reentry intervals or times" separate and distinct from preharvest intervals were necessary to protect the health of workers. At this time California is the only state establishing and enforcing its own reentry intervals. Reentry intervals, however, have been established by the EPA for the other states.

From 1949 through 1958, six multiple case poisoning incidents occurred in California involving at least 79 persons entering groves treated with ethyl parathion (Table 2). In 1959, 275 workers were poisoned in six separate citrus groves throughout the state (Table 2). An additional 87 workers were poisoned during the years 1961-1969. Two incidents involved azinphosmethyl and ethion, while the remaining illnesses were attributed to the use of ethyl parathion.

Quinby and Lemmon (1) studied these early poisoning episodes. They documented 11 episodes, 6 in the state of Washington and the balance in California. Dermal exposure was determined to be the likely route of exposure. In California, Milby et al. (2) studied the effects of organophosphorus pesticide residues on 186 peach orchard workers; percutaneous absorption of the oxidation products (oxons) of the organophosphorus esters was identified as the likely cause of the poisonings. From 1970 to 1972 there were nine episodes involving 86 persons poisoned with ethyl parathion in citrus groves in California.

This group of episodes led to the passage of legislation in California in 1972 establishing a Workers Health and Safety (WHS) group in the California Department of Food and Agriculture (CDFA) and the adoption of Worker Safety Regulations (3) involving reentry into crops treated with organophosphorus pesticides in cooperation with the California Department of Health Services (CDHS). The adoption of regulations and the formation of the Worker Health and Safety group provided the CDFA with the legal means to investigate illnesses, establish reentry intervals, and prosecute violators. At this time other states have not passed similar regulations or established enforcement agencies.

Since 1964, each poisoning incident in California has been investigated by the CDFA to determine the reasons for the occurrence and to identify ways to prevent such illnesses (Table 2). For example, the use of a new chemical, dialifor, on grapes in 1973-1974 resulted in illnesses among workers harvesting the grapes. A thorough investigation by the CDFA staff resulted in the establishment of a 75-day reentry interval and the eventual deregistration of dialifor in California (4-6). It was shown that the formation and percutaneous absorption of foliar residues of dialifor oxon were the principal reasons for the illnesses observed in the workers. Compliance with legally designated reentry intervals kept workers out of fields where excessive leaf residues were present.

Incidents of ethyl parathion poisonings in citrus groves during 1977, 1982, and 1985 were determined to be caused by the presence of high levels of paraoxon in soil dust underneath trees (7). Soil dust served as a vehicle for transferring paraoxon to the hands, arms, legs, and feet of workers harvesting fruit (8). Parathion and paraoxon residues on foliage were at levels considered to be safe for reentry as a result of compliance with long reentry intervals (3).

Immediately following the dialifor and several of the parathion illness incidents, harvesting was stopped, and large acreages of ripe fruit remained to be harvested. Analyses of residues in soil and on foliage were performed to identify treated fields safe to harvest. The guidelines used for determining a "safe" field residue are covered later in this chapter. Workers with normal red blood cell cholinesterase activity were placed under medical

supervision and allowed to return to work or quarantined until they were asymptomatic.

Whorten and Obrins (9) studied the effects of phosphamidon-treated citrus groves when reentry occurred. They found that when workers, their blood cholinesterase activity, and the workers could return to work before values return to normal. They also encountered with respiratory inhibition.

N-methylcarbamates (10) and (11). In a few instances, dizziness and resulted in the poisoning. In 1978, a date occurred in Indiana where a crew of 150 became ill after eating carbofuran (12). Sufficiently strong arms to produce the effect. In 1981, 4 out of 12 workers were applied to foliage less than 24 hours within a period of 4 or 5 days.

In addition to the foliar residues, it occasionally occurs in California from water from irrigation. In 1981, a worker seriously poisoned from oxamyl label to prevent

2.2 Field Reentry Studies

During the 1970s, several studies were conducted on a number of agricultural crops. Tobin (13) conducted studies on cotton treated with ethion 1 day before activity occurred. Reentry occurred before with azinphosmethyl. Cell cholinesterase activity into cotton previously treated with monocrotophos and ethion. Reentered treated cotton showed cholinesterase depression.

Spear et al. (19) conducted studies involving several applications of diazinon. Cholinesterase activity was depressed by 35% in workers. Response information on reentry periods for a number of crops. The results of the reentry studies on peaches. A reentry period of 72 hours. Reentry interval for azinphosmethyl discussed in Section 6, w

supervision and allowed to harvest these fields. Fields considered unsafe for harvest were quarantined until they were safe to reenter and harvest the crop (9).

Whorten and Obrinsky (10) studied a reentry poisoning incident involving mevinphos- and phosphamidon-treated row crops. Poisoning was induced by the parent compounds when reentry occurred illegally within 1–24 h after application. In order to protect workers, their blood cholinesterase levels were followed until values returned to normal and the workers could return to work. In some cases, a period of 3 months was needed before values return to normal levels. This illustrates the degree of interpersonal variability encountered with respect to exposure, percutaneous absorption, and cholinesterase inhibition.

N-methylcarbamates can cause cholinesterase inhibition when inhaled or ingested (11). In a few instances, dermal exposure to foliage, within 1 or 2 days after application, has resulted in the poisoning of field workers. The incident that involved the most injury to date occurred in Indiana in August 1974. Seventy-four young men and women of a work crew of 150 became ill while detasseling corn within 24 h of a foliar application of carbofuran (12). Sufficient carbofuran was absorbed through the skin of the hands and arms to produce the effects observed in these workers. Occasionally, other smaller scale incidents have been reported with *N*-methyl carbamates. For example, in the summer of 1981, 4 out of 12 workers in a California grape vineyard were poisoned by methomyl applied to foliage less than 24 h prior to reentry. The workers recovered from their illnesses within a period of 4 or 5 h.

In addition to the foliar residue problem with carbofuran and methomyl, poisoning occasionally occurs in California when uninformed persons enter a field or grove to drink water from irrigation equipment containing pesticides. Several persons have been seriously poisoned from ingesting oxamyl; reentry restrictions are now required on the oxamyl label to prevent such occurrences.

2.2 Field Reentry Studies

During the 1970s, several incidents with organophosphorus pesticides prompted a number of agricultural chemical companies to conduct medically supervised reentry studies. Tobin (13) conducted a study with workers harvesting fruit from a citrus grove treated with ethion 1 day prior to reentry. A reduction in red blood cell cholinesterase activity occurred. Reentry studies with workers reentering a peach orchard treated 1 week before with azinphosmethyl were conducted (14, 15). Here again, a reduction in red blood cell cholinesterase activity occurred in the workers. Studies involving workers and reentry into cotton previously treated separately with ethyl and methyl parathion (16) and monocrotophos and ethyl and methyl parathion (17, 18) were conducted. Workers reentered treated cotton fields 12–72 h after application of the pesticides. Red blood cell cholinesterase depression was detected in the workers.

Spear et al. (19) conducted an ethyl parathion field reentry study in citrus groves involving several application rates and reentry intervals. Cholinesterase activity was depressed by 35% in workers entering as late as 25 days postapplication. The dose-response information obtained in this study has been of considerable value in establishing reentry periods for a number of organophosphorus pesticides in California coupled with the results of the reentry studies conducted by Kilgore (20) involving azinphosmethyl on peaches. A reentry period of up to 90 days was established for parathion and a 14-day reentry interval for azinphosmethyl. The procedure for setting the reentry intervals is discussed in Section 6, which deals with the mathematics of setting safe levels on foliage.

2.3 Federal Reentry Standards

The Occupational Safety and Health Administration (OSHA) was the first federal agency to propose pesticide reentry standards to protect the health of farm workers (21). The first standards, adopted on May 1, 1973, included 21 organophosphorus insecticides and five crops (citrus, peaches, grapes, tobacco, and apples) in wet and dry areas. These standards were replaced 6 weeks later with less stringent standards covering only nine organophosphorus insecticides with intervals ranging from 1 to 3 days for wet areas and 14 days for dry areas (22).

During the summer of 1973, a jurisdictional dispute between the U.S. Environmental Protection Agency (EPA) and OSHA over which agency would set and administer reentry standards occurred and was finally resolved in Federal Court in favor of the EPA. A year later the Federal Working Group on Pest Management appointed T. H. Milby to chair a Task Group on Occupational Exposure to Pesticides (23). The Task Group recommended that registrants should be required to (i) submit data to the EPA for establishing reentry intervals and (ii) pay attention to geographical differences and that (iii) the Federal Government should support research into the fundamental factors that influence reentry intervals with respect to farm worker safety.

In the *Federal Register* on March 11, 1974 (24), the EPA published 48-h reentry standards for 11 organophosphorus insecticides, endrin, and endosulfan. The regulations also recognized state responsibility and authority to set additional restrictions to meet local problems as carried out by the California Department of Food and Agriculture. In order to develop reentry intervals, the CDFA put into place monitoring requirements based on the recommendations of the California Department of Health Services (25). These monitoring studies utilized changes in field worker blood cholinesterase levels to determine if dislodgeable residues were at a "safe level." Since these requirements included the use of human subjects (i.e., field workers), the studies were to be conducted in a manner conforming to ethical requirements involving medical supervision and the safeguarding of the individual subject's safety and dignity.

Several well-controlled reentry studies were conducted by Knaak et al. (26) and Pependorf et al. (27), respectively, with phosalone on citrus and peaches in California. The study by Knaak and co-workers followed conventional field workers while the study by Pependorf followed college students working as fruit pickers. The results of these studies provided useful information for establishing reentry intervals for phosalone. None of the workers entering groves after the application of phosalone developed cholinesterase poisoning symptoms or a decrease in red blood cell cholinesterase activity.

The monitoring requirements were later modified in 1975 to exclude the use of farm workers as subjects in monitoring studies. This policy was based on the contentions that under the current conditions in California agriculture, truly informed and voluntary consent, free from any duress, could not be obtained from farm field workers. In a meeting of CDFA and EPA officials held in San Francisco in 1977, the Federal Government took the position that California's approach to establishing reentry intervals used human subjects in a manner inconsistent with the current views of the Federal Agency concerning informed consent as covered in the Guidelines for Protection of Human Subjects (28) promulgated by the U.S. Department of Health, Education, and Welfare. The use of animal models was recommended as a means for obtaining the necessary data for setting reentry intervals.

In 1980, the EPA presented a new set of methodologies for setting reentry intervals (21). Three types of data were determined to be necessary to calculate a reentry interval:

(i) dose-response exposure and (iii) (AEL) was determined in the *Assessment Guidelines* document involving cholinesterase.

3 HAZARD

A chapter on the discussion of the pesticides, their effects on cholinesterase response in field workers and determining safe levels.

3.1 Properties

The organophosphorus in red blood cells. Organophosphorus irreversibly phosphorates are produced as phosphorothioate phosphonates. The dimethyl, dialkyl phosphorates produce more toxic oxons are better in the principal reaction.

The insecticide acetylcholinesterase complex is unstable.

The poisoning of carbamate esters system. Red blood animals are routinely nervous system cholinesterase inhibitors produce cholinesterase activity.

Recovery of A synthesis of new esters of the phosphorylated carbamylated reviewed by Hirsch.

Blood cholinesterase worker exposure

(i) dose-response data, (ii) estimates of a relation between surface residues and total body exposure and (iii) time versus residue data. In this procedure an allowable exposure level (AEL) was determined. In 1984 the EPA published the methodologies in detail in *Pesticide Assessment Guidelines, Subdivision K, Exposure: Reentry Protection* (12). The reentry study involving chlordiophos presented in Section 6 of this chapter is referenced in this document.

3 HAZARD EVALUATION

A chapter on the pesticide field reentry problem would not be complete without a brief discussion of the toxic properties of the organophosphorus and *N*-methylcarbamate pesticides, their action on acetylcholinesterase, bioassay procedures used to determine their effects on circulating red blood cell cholinesterase, procedures for measuring dermal dose-ChE response, and percutaneous absorption in model animals. The automated cholinesterase procedure described in Section 3.2 was used to detect these pesticides in field workers and in model animals. These procedures play an important role in determining safe level for organophosphorus esters and *N*-methylcarbamates on foliage.

3.1 Properties of Toxic Organophosphorus and Carbamate Esters

The organophosphorus pesticides inhibit acetylcholinesterase in the nervous system and in red blood cells of humans and animals by reacting with the active site of this enzyme. Organophosphorus insecticides vary in their affinity for the enzyme and in their ability to irreversibly phosphorylate the enzyme (29). Six types of organophosphorus insecticides are produced and used in the United States and are represented by phosphates, phosphorothioates, phosphorothiolates, phosphorodithioates, phosphoroamidates, and phosphonates. The phosphorothioates (parathion) and phosphorodithioates (azinphosmethyl, dialifor, methidathion, dimethoate, and phosalone) are oxidized on foliage to produce more toxic products called oxons (phosphates and phosphorothioates). The oxons are better inhibitors of acetylcholinesterase and their formation on plant foliage is the principal reason for the reentry poisoning in California (23).

The insecticidal carbamates, esters of *N*-methylcarbamic acid, are also inhibitors of acetylcholinesterase. They vary in their affinity for the enzyme. The enzyme-inhibitor complex is unstable, resulting in the release of the intact carbamate and enzyme (11).

The poisoning symptoms observed in workers exposed to organophosphorus and carbamate esters were caused by the inhibition of acetylcholinesterase in the nervous system. Red blood cell cholinesterase activity measurements in workers and experimental animals are routinely used to estimate indirectly the in vivo effects of these pesticides on nervous system cholinesterase. According to studies in the rat, administration of AChE inhibitors produces an almost immediate decrease in both red blood cell and brain cholinesterase activity.

Recovery of AChE activity, inhibited by organophosphorus esters, occurs by direct synthesis of new enzyme, dissociation of the enzyme-inhibitor complex and reactivation of the phosphorylated enzyme, or in the case of the carbamates mainly by reactivation of the carbamylated enzyme. Poisoning and the treatment of poisoning were recently reviewed by Hirschberg and Lerman (30) and Lerman et al. (31).

Blood cholinesterase activity assays are the principal procedures used to determine worker exposure to cholinesterase inhibitors and to examine the dermal dose-ChE

response relation in animal models. The blood cholinesterase assay is discussed in Section 3.2 of this chapter.

Technical organophosphorus (OPs) and *N*-methylcarbamate insecticides respectively, are supplied by manufacturers as viscous liquids and crystalline solids to be formulated with organic solvents, detergents, and water as emulsifiable concentrates or as water-soluble powders for dilution in water for application (32). Most of these materials are strongly lipophilic. Exceptions, however, exist as a number of the OPs and *N*-methylcarbamates are quite water soluble. Acephate is a white solid material, soluble to 65% w/v in water and to only 10% w/v in acetone-ethanol and 5% w/v in aromatic solvents. Its hydrolysis product, methamidophos, is even more water soluble than acephate and less soluble in organic solvents. Methomyl, a white crystalline *N*-methylcarbamate used extensively in agriculture, is soluble in water to the extent of 5.8% w/v in water and 100% w/v in methanol. Oxamyl, closely related in structure to methomyl, is even more soluble in water, 28% w/v, and methanol, 144% w/v.

The organophosphorus insecticides vary in their acute oral toxicity from less than 1.0 mg/kg of body weight for the most toxic oxons such as paraoxon to well over 1500 mg/kg for the less toxic OPs (e.g. malathion). The *N*-methylcarbamates also vary widely in their acute oral toxicities, which range from a low of 8.0 mg/kg (aldicarb) to several hundred mg/kg (i.e., carbaryl).

Field workers, however, are dermally exposed to residues of organophosphorus and carbamate insecticides on foliage. The EPA regulations (33) currently group pesticide products into three toxicity categories based on the results of dermal LD₅₀ studies in the rabbit. Category I materials have a dermal LD₅₀ of <200 mg/kg, category II materials a dermal LD₅₀ of 200-1000 mg/kg, and category III materials a dermal LD₅₀ of >1000 mg/kg. The oxons formed from the phosphorothioates and phosphorodithioates have a dermal LD₅₀ of <200 mg/kg. Reentry intervals may be required by EPA (12) and the California Department of Food and Agriculture (34) for pesticide products assigned to categories I and II. The relation between a dermal dose of an organophosphorus or carbamate ester and its effect on blood cholinesterase activity is discussed in Section 3.3 and used in Section 6 of this chapter to set reentry intervals.

3.2 Blood Cholinesterase Assay

The Milby report (23) recommended the use of the Michel (35), pH-Stat (Nabb and Whitfield, (36) or colorimetric method (Ellman et al., 37) for measuring blood cholinesterase activity of field workers. The pH-Stat and colorimetric methods are suitable for measuring the inhibitory action of organophosphorus and carbamate esters, while the Michel method was found suitable only for organophosphorus esters. Long incubation periods at high pH resulted in the reactivation of cholinesterase. All three methods were manual methods requiring a substantial amount of time and effort to obtain reproducible results. The automated Ellman method of Humiston and Wright (38) was modified by Knaak et al. (39) to run on the Technicon Auto Analyzer II system. This two-channel system uses in one channel whole blood (intact red cells) or plasma as enzyme, acetylthiocholine as substrate, and a dialyzer system to separate the enzyme from the hydrolysis product, thiocholine, prior to reacting DTNB [5,5-dithiobis(2-nitrobenzoic acid)] with thiocholine to produce a yellow color. The second channel blanks out color resulting from nonenzymatic hydrolysis of acetylthiocholine.

The cholinesterase activity of the red blood cells is obtained by subtracting the activity

of the plasma

RB

The activity c
—SH release
Company, St.
the instrumen
diluted 1:6 wi
dlose—ChE res
1:3.5 with bu
standards are
method is beir
clinical labora

3.3 Derma

The field reen
relation betwe
to set safe reen

Figure 1. Derma
to the clipped b
determined after
RBC ChE activ
Contamination a

of the plasma from the activity of whole blood using the sample's hematocrit in Eq. (1):

$$RBC = \frac{\text{whole blood activity} - \left(\frac{1 - \text{hematocrit}}{100}\right)(\text{plasma activity})}{\text{hematocrit}/100} \quad (1)$$

The activity of whole blood, RBCs, and plasma are reported in terms of micromoles of —SH released per minute per milliliter of sample. Plasma from Sigma Chemical Company, St. Louis, Missouri is used as the enzyme standard and reduced glutathione as the instrument standard. In field worker studies involving human blood, whole blood was diluted 1:6 with pH 7.7 buffer and plasma was diluted 1:3 with buffer, while in the dermal dose—ChE response studies discussed in Section 3.3 whole blood from the rat was diluted 1:3.5 with buffer, while plasma was used without dilution. The results with enzyme standards are reproducible from run to run. After 10 years of field and laboratory use, the method is being considered by the California Department of Health Services as an official clinical laboratory method.

3.3 Dermal Dose—ChE Response

The field reentry studies involving farm field workers were conducted to determine the relation between foliar pesticide residues in $\mu\text{g}/\text{cm}^2$ and cholinesterase depression in order to set safe reentry intervals. These studies were costly and often provided little information

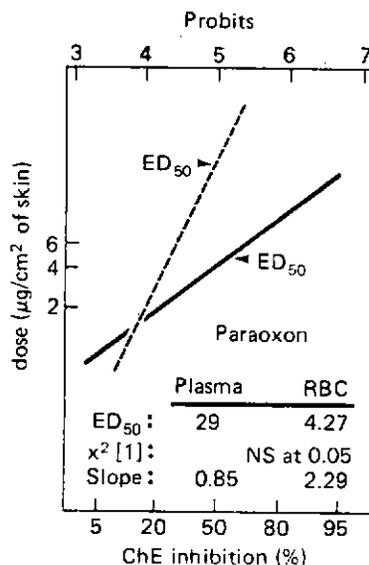


Figure 1. Dermal dose—ChE response curves obtained for paraoxon in the rat. Paraoxon was applied to the clipped backs (25 cm²) of 220–240-g male Sprague-Dawley rats. Blood ChE activity was determined after 72 h of exposure. Figure taken from Knaak et al. (42). ---Plasma ChE activity; — RBC ChE activity. (Reprinted with permission from Springer-Verlag, *Bulletin of Environmental Contamination and Toxicology*.)

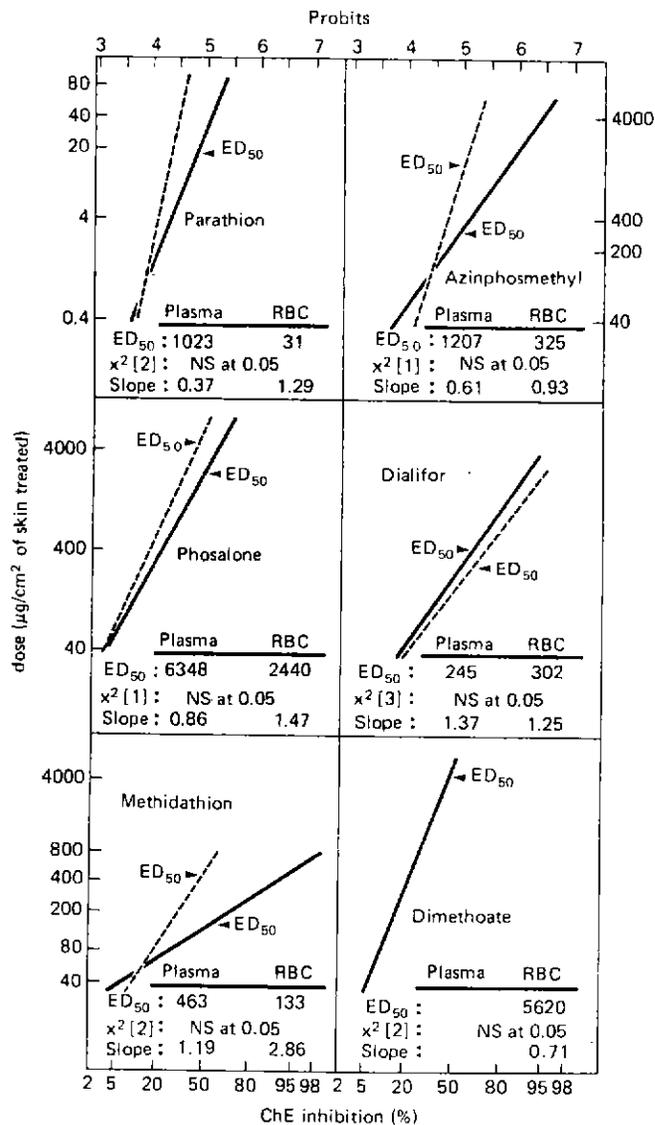


Figure 2. Dermal dose-ChE response curves for six organophosphorus pesticides. Male Sprague-Dawley rats weighing 220-240 g were used. A 25-cm² area of back skin was treated. Blood ChE activity was determined after 72 h of exposure. ---, Plasma ChE; —, RBC ChE. Figure taken from Knaak et al. (42). (Reprinted with permission from Springer-Verlag, *Bulletin of Environmental Contamination and Toxicology*.)

relating foliar residue levels we

Gaines (40, 41) found that 4 mg/kg of body weight of data were, it could be used to estimate cholinesterase in curves (ED₅₀) in for a number of dermal dose-response curves for dialifor, phosalone resulting in 50% inhibition is given along with simulated a 3-day (42, 43) to establish these cholinesterase

This work with carbamates, used to estimate foliar levels and dermal dose-ChE response curves are given

The dose-re-

Figure 3. Dermal dose-ChE response curves for six organophosphorus pesticides. Male Sprague-Dawley rats weighing 220-240 g were used. A 25-cm² area of back skin was treated. Blood ChE activity was determined after 72 h of exposure. ---, Plasma ChE; —, RBC ChE. Figure taken from Knaak et al. (42). (Reprinted with permission from Springer-Verlag, *Bulletin of Environmental Contamination and Toxicology*.)

relating foliar residue data to cholinesterase inhibition, because exposure times and foliar residue levels were not sufficient in magnitude to produce a dose-related effect in workers.

Gaines (40, 41) was the first to develop extensive acute dermal toxicity (LD_{50}) data in mg/kg of body weight on organophosphorus pesticides in the rat. As good as the mortality data were, it could not readily be used to relate residue levels or dermal dose in $\mu\text{g}/\text{cm}^2$ to cholinesterase inhibition. Knaak et al. (42) were the first to develop dermal dose-response curves (ED_{50}) in the rat relating dose in $\mu\text{g}/\text{cm}^2$ of skin surface to cholinesterase inhibition for a number of the organophosphorus pesticides of interest. Figures 1 and 2 give the dermal dose-response curves obtained by Knaak et al. (42) for paraoxon, parathion, dialifor, phosalone, azinphosmethyl, dimethoate, and methidathion. The dose (ED_{50}) resulting in 50% red blood cell and plasma cholinesterase inhibition after 72 h of exposure is given along with the slopes of the log-probit regression lines. The 72-h exposure period simulated a 3-day harvesting period. The results of these studies were used by Knaak et al. (42, 43) to establish safe levels on tree foliage (in $\mu\text{g}/\text{cm}^2$). Pependorf and Leffingwell (44) used these cholinesterase inhibition data to develop their "unified field model."

This work was extended by Knaak et al. (45) to include several important *N*-methyl carbamates, used extensively in California agriculture, for the purpose of establishing safe foliar levels and reentry intervals as described for organophosphates in Section 6.1. The dermal dose-ChE response curves for methomyl, thiodicarb, methiocarb, and methiocarb sulfoxide are given in Figs. 3 and 4.

The dose-response curve for methomyl is included with the curve for thiodicarb,

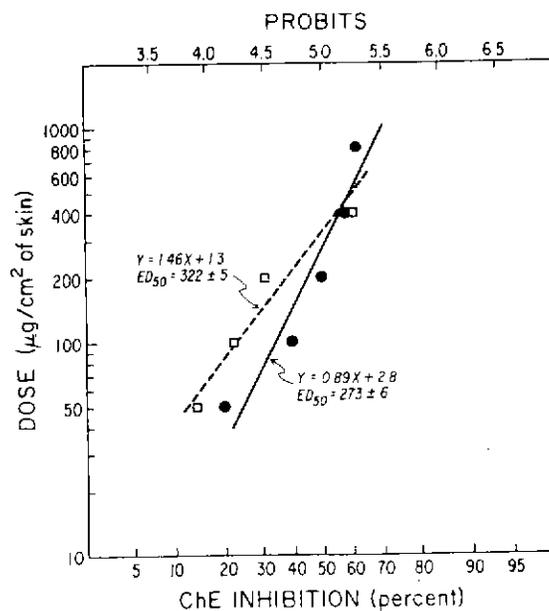


Figure 3. Dermal dose-ChE response curves for thiodicarb and methomyl. Male Sprague-Dawley rats weighing 220-240 g were used. A 25-cm² area of back skin was treated. RBC blood ChE activity was determined after 24 h of exposure. ---, Thiodicarb; —, methomyl. Figure taken from Knaak et al. (45). (Reprinted with permission from American Chemical Society book publications.)

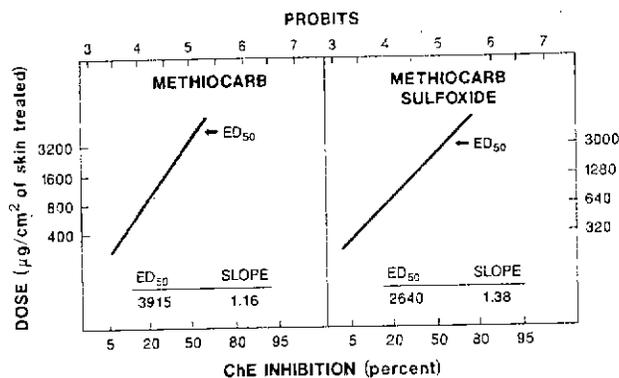


Figure 4. Dermal dose-ChE response curves for methiocarb and methiocarb sulfoxide. Male Sprague-Dawley rats weighing 220–240 g were used. A 25-cm² area of back skin was treated. Red cell ChE activity was determined after 24 h of exposure. Figure taken from Knaak et al. (45). (Reprinted with permission from American Chemical Society book publications.)

because of their structural similarities. Thiodicarb may be described as a molecule of methomyl linked to a second molecule of methomyl via an N-S-N bridge. In the rat, thiodicarb is metabolized to methomyl. The dermal dose-ChE response curves indicate that these two pesticides are similar in their ability to produce cholinesterase inhibition when topically applied. This is surprising, because they possess different physical properties. Methomyl is soluble in water to the extent of 5.8% w/v, while thiodicarb is virtually insoluble in water and organic solvents. Safe levels were determined for both methomyl and thiodicarb using the procedure of Knaak et al. (42).

3.4 Percutaneous Absorption

A number of dermatopharmacokinetic studies were conducted using radiolabeled organophosphorus and carbamate pesticides (46, 47) to determine the fate of pesticides. A few of these studies were conducted in conjunction with dermal dose-cholinesterase response studies to provide kinetic as well as cholinesterase inhibition data.

The fate, absorption kinetics, and dermal dose-ChE response of topically applied [ring-U-¹⁴C]parathion, [ring-U-¹⁴C]carbaryl, and [acetyl-1-¹⁴C]thiodicarb were studied by Knaak et al. (46, 47). According to these studies, a 40-µg/cm² dose of parathion is absorbed at the rate of 0.5 µg/h·cm². The retention time on skin, $t_{1/2}$ = 24.3–28.6 h, was less than its half-life, 28.5–39.5 h, in plasma.

Carbaryl was not absorbed as readily as parathion. The retention half-life for a 40-µg/cm² topical dose was 40 h, while the $t_{1/2}$ for elimination from plasma was 67 h. Thiodicarb dissipated at an initial rate (0–24 h; $t_{1/2}$, alpha phase) of 40 h from the skin of adult female rats and at a final rate (24–167 h; $t_{1/2}$, beta phase) of 254 h. Thiodicarb equivalents were at plateau levels in plasma during the study. The time-concentration curves for the absorption and elimination of [¹⁴C]parathion and [¹⁴C]carbaryl in selected tissues are given in Figs. 5 and 6. The time-course recoveries of dermally applied ¹⁴C-labeled parathion, carbaryl, and thiodicarb are shown in Fig. 7. The model given in Fig. 8 describes the overall absorption and elimination of a topically applied dose. Maibach

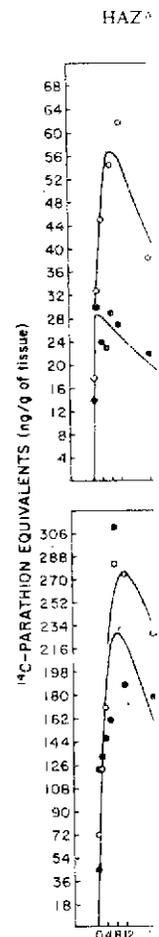


Figure 5. Time-concentration curves for [¹⁴C]parathion equivalents (ng/g of tissue) in selected tissues. Figure taken from Knaak et al. (46). (Reprinted with permission from American Chemical Society book publications.)

et al. (48) studied the absorption of parathion in human volunteers. A 5-day study was conducted in which parathion was topically applied to the skin of human volunteers.

The results of parathion absorption in human volunteers of various ages are given in Table I. The results show that the absorption of parathion is higher in young females than in adult males.

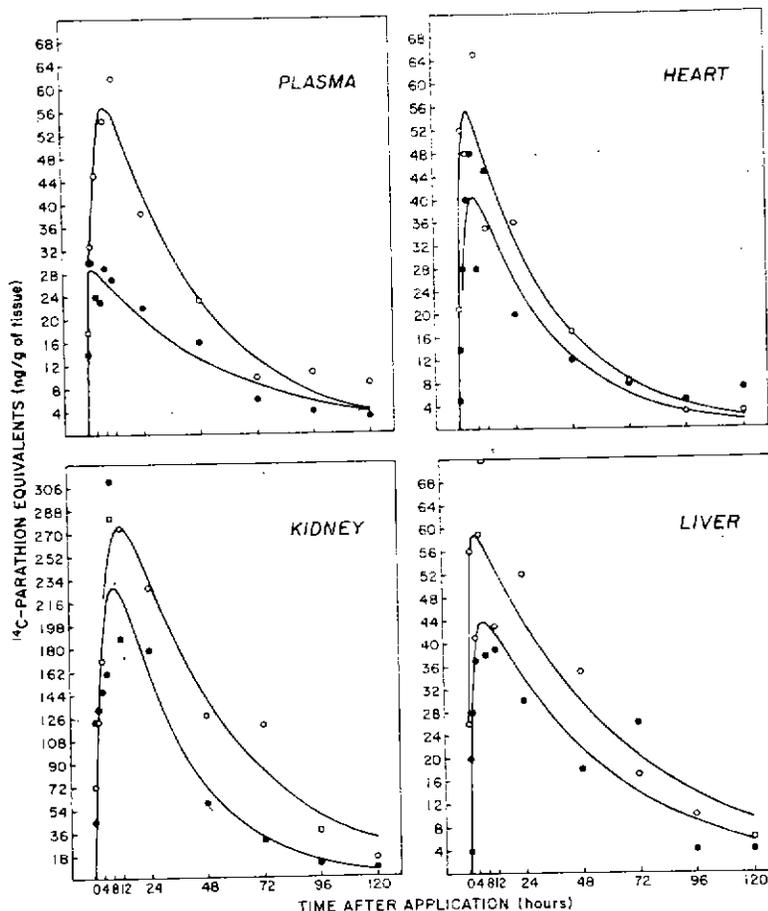


Figure 5. Time-concentration curves for the simultaneous absorption and elimination of [^{14}C]parathion equivalents in plasma, heart, kidney, and liver. ●, Adult males; ○, adult females. The mean coefficient of variation for the tissue values at each time interval was 37%. Figure taken from Knaak et al. (46). (Reprinted with permission from Academic Press, *Toxicology and Applied Pharmacology*.)

et al. (48) studied the absorption of [^{14}C]parathion and [^{14}C]carbaryl in human volunteers. A 5-day period was required to achieve a completely absorbed and eliminated topically applied dose. The studies indicated that carbaryl was more readily absorbed than parathion.

The results of parathion dermal dose-ChE response studies in male and female rats of variable age are given in Table 3. Blood samples were taken and analyzed for red blood cell cholinesterase activity 72 h after the application of the dose. Parathion was more toxic to females of varying ages than to males, and less toxic to young animals, on a weight basis. On a surface area basis, parathion was more toxic to females than males, equally toxic to young and adult males, but less toxic to young females, than adult females. Carbaryl at

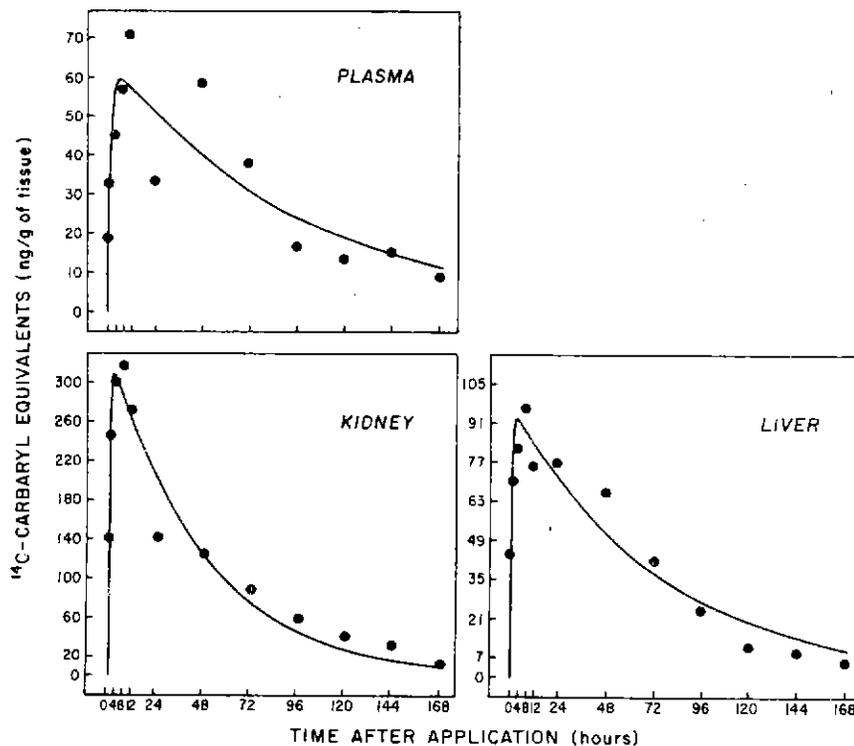


Figure 6. Time-concentration curves for the simultaneous absorption and elimination of [¹⁴C]carbaryl equivalents in plasma, kidney, and liver of adult male rats. The mean coefficient of variation for the tissue values at each time interval was 27%. Figure taken from Knaak et al. (46). (Reprinted with permission from Academic Press, *Toxicology and Applied Pharmacology*.)

dose levels as high as 4000 $\mu\text{g}/\text{cm}^2$ of skin did not inhibit red blood cell ChE activity 24 h after the application of the dose even though it was absorbed through skin. According to these absorption studies, the nature of the chemical, the nature of the skin and skin site, the size of the exposure area, the concentration on skin (in $\mu\text{g}/\text{cm}^2$), and the time are the major factors governing the amount of pesticide absorbed.

4 EXPOSURE ASSESSMENT

The development of the dislodgeable residue methodology and procedures for measuring the transfer of pesticide foliar residues to workers provided the environmental data for estimating dermal dose.

4.1 Dislodgeable Leaf Residue Methodology

4.1.1 Application of Pesticides to Small Plots. The maximum hazard that a worker might encounter in a treated field is typically estimated by applying the maximum

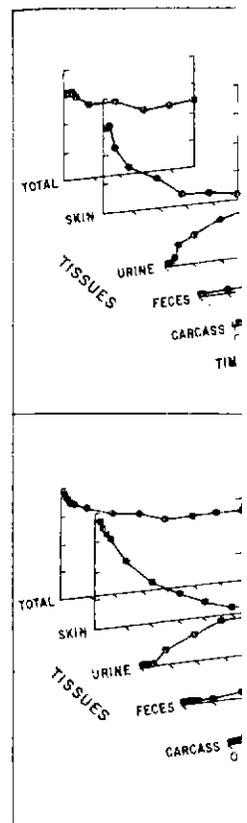


Figure 7. Time-concentration curves for the simultaneous absorption and elimination of [¹⁴C]carbaryl equivalents in peritoneal fluid, urine, feces, carcass, and tissues of adult male rats after application. Figure taken from Knaak et al. (46). (Reprinted with permission from Academic Press, *Toxicology and Applied Pharmacology*.)

APPLIED
SKIN SURF

Figure 8. Two-compartment model for the absorption and elimination of pesticides from the skin which takes up the pesticide. Figure taken from Knaak et al. (46). (Reprinted with permission from Academic Press, *Toxicology and Applied Pharmacology*.)

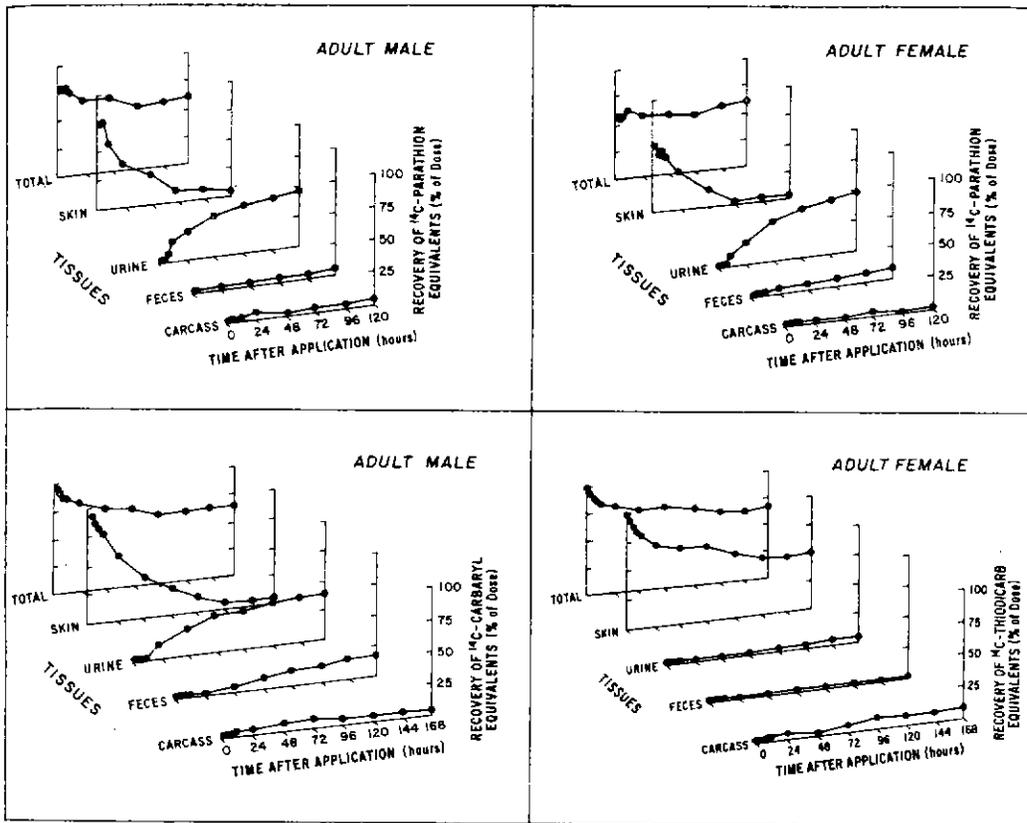


Figure 7. Time-course recovery of topically applied ^{14}C -labeled parathion, carbaryl, and thiodicarb equivalents in percentage of dose in feces, urine, carcasses, and skin (surface and penetrated residues) after application. Figure taken from Knaak and Wilson (47). (Reprinted with permission from American Chemical Society book publications.)

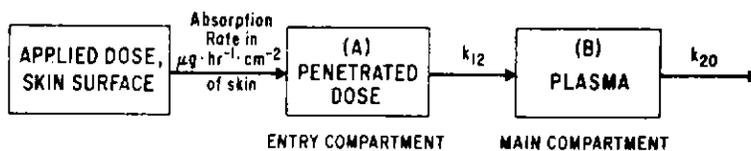


Figure 8. Two-compartment model with a central compartment (B) and an entry compartment (A) which takes up the topically applied dose. Figure taken from Knaak and Wilson (47). (Reprinted with permission from American Chemical Society book publications.)

TABLE 3. Parathion: Dermal Dose-Red Cell ChE Response in Male and Female Rats of Variable Age^a

| Sex, Age, Weight ^b | Slopes | ED ₅₀ (μg/cm ² of treated area) ^c | ED ₅₀ (μg/cm ² of total body surface) ^c | ED ₅₀ (mg/kg of body weight) |
|-------------------------------|--------|--|--|---|
| M, 10 weeks, 296 g | 1.7 | 24.3 ± 3.7 | 1.7 ± 0.3 | 2.4 |
| M, 5 weeks, 145 g | 1.3 | 22.7 ± 4.2 | 1.6 ± 0.3 | 2.9 |
| F, 13 weeks, 279 g | 1.9 | 14.0 ± 3.7 | 1.0 ± 0.3 | 1.4 |
| F, 5 weeks, 147 g | 1.5 | 19.0 ± 4.1 | 1.3 ± 0.3 | 1.8 |

^aTotal area treated (7% of body surface).

^bSprague-Dawley rats, Simonsen, Gilroy, CA.

^cValues given with 95% confidence limits.

Source: Knaak et al. (46).

registered or proposed label rate, even though the normal use rate may be lower. The equipment used for the pesticide application should be typical of that used by the growers. The method of application should be selected such that the maximum foliar residue results. For example, the maximum label rate can often be applied to citrus trees by using either an oscillating boom sprayer or an airblast sprayer. Because the amount of water used with an oscillating boom sprayer may be on the order of 1500 gal/acre while that for an airblast sprayer is about 100 gal/acre, the amount of pesticide deposited on the outer foliage is different for the two applications. Airblast applications deposit more pesticide than boom applications.

The selection of the size of the test plot should be based on the ability to simulate an actual pesticide application made by a commercial operator. Ideally, the plot should be part of a larger field of the same crop so that the environmental conditions are representative of the crop. An isolated row of citrus, for example, would experience different climatic conditions than a row of citrus located within a grove of similar trees. If climatic factors, such as low humidity and high solar radiation, are believed to produce additional toxic residues such as organothiophosphate oxygen analogues (oxons), pesticide applications should be made in typically hot geographic regions and months of the year. However, the geographic region and time of year should not be atypical for the treated crop or the pesticide used, so as to produce atypical results of pesticide residues.

4.1.2 Development of the Leaf-Punch Sampler. Pesticide residue data are generally expressed in terms of weight of pesticide per unit weight of matrix, such as micrograms per gram of soil, or weight of pesticide per unit volume of matrix, such as micrograms per liter of water. In both cases, one is interested only in the ratio of the amount of pesticide to the amount of matrix. When attempting to assess the hazards of reentry, it was recognized that only that portion of the total residue which was transferable to the worker was of concern. Pesticide residues inside plant tissues or surface waxes are not available to the agricultural worker, except through ingestion of the plant part, and therefore need not be considered. Conversely, pesticide residues on the plant surfaces are clearly the chief concern.

Residues may also be present as a liquid or solid pesticide deposit on the leaf surface, or they can be present in dust particles or clay particles, especially when they are used as formulation carriers. In general, surface residues require a surface area measurement so that the amount of pesticide can be reported on a per unit area basis, such as micrograms per square centimeter. Because foliage was initially suspected as the primary source of pesticide exposure, a technique to measure contamination was needed. An estimation of

leaf area w
workers (5
standard s
collected, t
punch sam
residue an

Two di
sampling
thinner na
and the n
disturbanc
designed s
shear the l

leaf area was possible using templates, but it was impractical. However, Gunther and co-workers (50) recognized that leaves, analogous to sheets of paper, could be punched in standard sizes. By knowing the aperture of the leaf punch and the number of leaf disks collected, the total area represented by the sample can readily be calculated. Thus, the leaf-punch sampler was developed as the tool of choice for collecting samples of foliage for residue analysis (50).

Two different apertures were initially used. A 2.5-cm (1-in.) aperture was used for sampling citrus leaves. A 1.8-cm aperture was used for peach leaves to accommodate the thinner nature of these leaves compared to citrus and grape leaves for excising purposes and the narrower nature of peach leaves. The punch had a concave surface to avoid disturbance of the surface residues. Unlike later leaf punches, the earlier models were designed so that the punch rotated one-eighth of a turn during the downward stroke to shear the leaf tissue and enhance the excision process. The first leaf punch was based on the

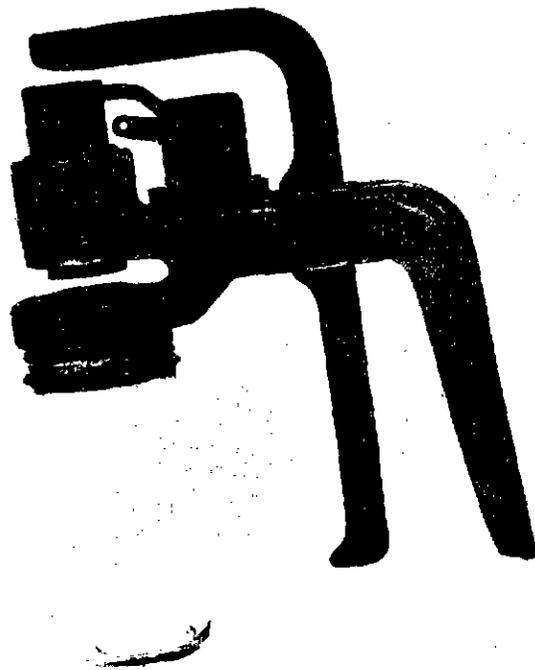


Figure 9. Punch for obtaining leaf disks for analysis of dislodgable residues.

basic design of Smith and Little (51) and was privately manufactured by Norman Willett. Currently, leaf-punch samplers are available from Birkestrand Company (2563 Loma Avenue, South El Monte, CA 91733). A photograph of the leaf-punch sampler is shown in Fig. 9.

The simplicity of this sample collection procedure allowed the collection of a large number of leaf disks per treated field. Both statistically adequate sample size and appropriate field representation can easily be achieved. A collection jar for the sample simply screws onto the sampler and is replaced with a clean jar after each batch sample has been collected (Fig. 9). The jar containing the sample is simply capped and returned to the laboratory. An 8-oz jar is recommended to reduce the likelihood that the leaf disks will remain clumped together during the dislodgeable residue removal step.

4.1.3 Collection with the Leaf-Punch Sampler. Leaf-disk samples are collected such that representative samples are obtained. In the case of tree crops, leaf disks are collected such that leaves from each octant around the tree are sampled equally by using eight or more trees. For row crops such as grapes, random samples from various heights are collected from a representative length of a field row. The primary objective is to collect samples from the type of foliage from which the worker will obtain the most contact or residues. A set of 40 disks per sample and three field replicates is deemed adequate. A stroke-activated counter on the leaf-punch sampler is used to keep track of the number of leaf disks collected. Variation among field replicates averages about 15%.

Field experience has demonstrated that the cutting edge needs to be cleaned after each batch sample with a tissue paper or a cotton swab moistened with water or acetone to remove plant juices, to maintain easy operation of the punch and to prevent cross-contamination between samples. It is best not to rely solely on the stroke-activated counter but to keep track mentally of the number of leaves sampled. The leaves should be free of excess moisture at the time of sampling; moisture resulting from a spray application, rain, overhead sprinkler irrigation, or morning dew should be allowed to evaporate before sampling is undertaken. Sample storage has been addressed by Gunther et al. (52).

4.1.4 Removal of Dislodgeable Residues. The dislodgeable residue procedure involves the removal of surface residues by shaking the leaf disks with a dilute aqueous surfactant solution. The surfactant used was the American Cyanamid Company's Sur-Ten consisting of sodium dioctylsulfosuccinate. The first published procedure gave instructions that the leaf-disk sample be first shaken with 50 mL of the surfactant solution for 1 h and then with 50 mL of fresh solution for 30 min, and finally with 25 mL of solution for 5 s. The three wash solutions were combined in a separatory funnel and extracted with an organic solvent to recover the pesticide. This residue removal procedure with some variations has become a standard method for recovering dislodgeable residues (53).

4.1.5 Plotting Results and Determining the Half-Life of Residues. Following application, the dissipation of dislodgeable residues from foliage is a complex process. It is dependent on the chemical and physical properties of the pesticides and their alteration products. If the logarithm of the residue is plotted against time, the dissipation process appears to have as many as three distinct parts. During the initial 1–3 days after application, residues may decline at a very rapid rate. Pesticides may be lost through volatilization along with the water used as a diluent or may penetrate into plant tissues. Between 1 day and 3 weeks after application, there is a much slower loss of residues. Then finally, after 3–4 weeks after application there is a very slow loss of residues. The entire

dissipation of
hydrocarbon

4.2 Exampl

Dissipation c
are given, res
parathion w
residues cont
This high pe
episodes asse
with the form
et al., 55). At
oxygen anal
application t
oxon lost ma
parent insect
oxon being f

Figure 10. D
by gas chrom
parathion/160
from America

dissipation process is influenced by the presence of water, surfactants, emulsifiers, hydrocarbons, clays, and other materials present in the formulations.

4.2 Examples of Dislodgeable Residue Dissipation Curves

Dissipation curves for foliar applications of parathion, azinphosmethyl, and methidathion are given, respectively, in Figs. 10, 11, and 12. Paraoxon was formed on citrus foliage from parathion within the first 3 days postapplication (Gunther et al., 54). Whereas parathion residues continued to decline, paraoxon residues appeared to remain stable on the foliage. This high persistence of a very toxic compound was the main reason for the poisoning episodes associated with this pesticide. Azinphosmethyl dissipated more slowly on citrus with the formation of its oxygen analogue at the 6-1b AI/acre application rate (Kvalvag et al., 55). At lower rates of application, the oxon of azinphosmethyl was not detected. The oxygen analogue of methidathion was formed from the parent compound shortly after its application to citrus foliage (56). As the level of parent insecticide declines, the amount of oxon lost matched the amount formed and led to a "steady-state" residue level. When the parent insecticide reached lower levels, oxon dissipation was not offset by any additional oxon being formed and the oxon level declined.

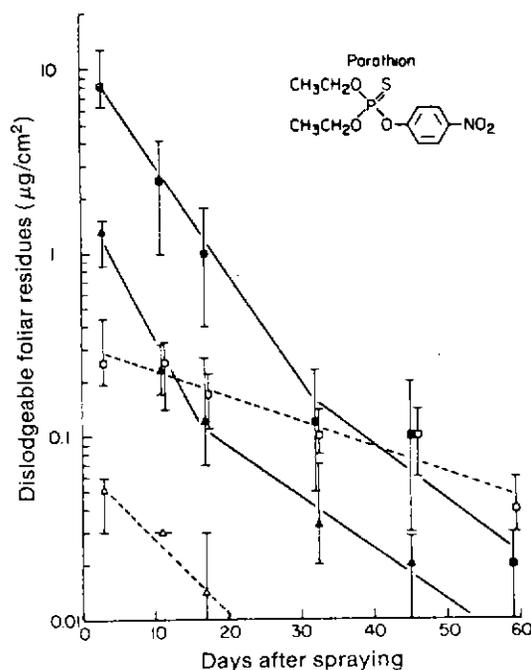


Figure 10. Dissipation of parathion (closed symbols) and paraoxon (open symbols) on orange trees by gas chromatography. ■, and □, 10 lb AI parathion/100 gal per acre; ▲ and △, 10 lb AI parathion/1600 gal per acre. Figure taken from Knaak and Iwata (71). (Reprinted with permission from American Chemical Society book publications.)

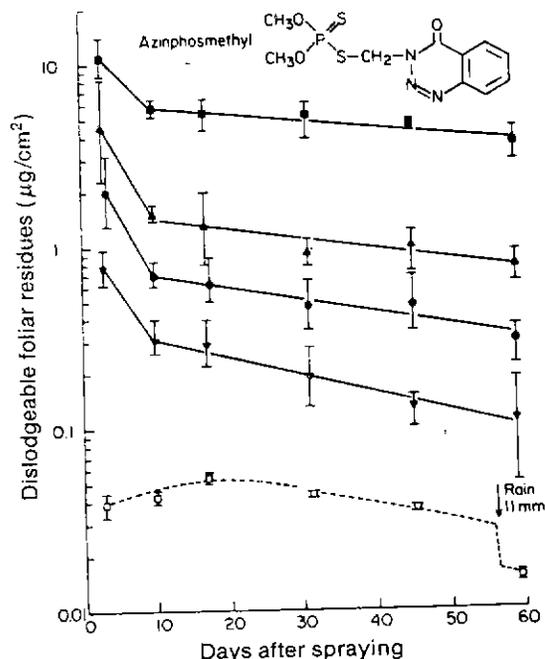


Figure 11. Dissipation curves for dislodgeable foliar residues of azinphosmethyl after a Guthion 2EC application to orange trees at 6 lb AI/100 gal (■) and at 6 lb AI/1200 gal (▲) per acre and at 2 (●) and 1 (▼) lb AI/500 gal per acre. Azinphosmethyl oxon (□) was determined only at the 6-lb AI/100 gal per acre treatment rate. Vertical lines give the range of values for six field sample replicates analyzed for azinphosmethyl and two field sample replicates analyzed for oxon. Data from Gunther et al. (54) and Kvalvag et al. (55). (Reprinted with permission from American Chemical Society book publications.)

4.3 Transfer of Foliar Residues to Workers

Investigative studies dealing with the hazards to workers contacting foliar residues of organophosphorus pesticides (OPs) principally involve ethyl parathion (Spear et al., 19), dioxathion (57), and phosalone (27) in California. Milby et al. (2) and Westlake et al. (57) estimated dermal exposure by washing unabsorbed residues from skin and measuring the residues in the washings by gas chromatography or by estimating the dermal dose indirectly from the amount of dust removed by scrubbing and rinsing skin, assuming that the pesticide concentration on skin was equal to the concentration in foliar dust.

The present and currently most acceptable method for measuring the dermal dose makes use of a multilayered cloth patch attached to skin or clothing to collect residues. The method was first used by Durham and Wolfe (58) in their investigations. Exposure patches consisted of 10.2 cm × 10.2 cm (4 in. × 4 in.) glassine weighing paper backing, a 4 in. × 4 in. alpha-cellulose center, and a 10-ply 4 in. × 4 in. surgical sponge outer dust collection medium. The patches are attached on the inside or outside of clothing, on both shoulders, chest, back, both forearms, and both upper arms, thighs, and shins. Residues on the hands are collected by washing the hands with soap and water or using alcohol.

Popendorf and Leffingwell (44) published the first quantitative model that relates field

Figure 12. Dissipative methidathion oxon (gal (■, □) and 5.6 lb six field sample repl Chemical Society bo

worker exposure t from a series of f parathion, and me commercial equipr dermal patches we after application. F the day and analyz During each work being harvested. T Gunther et al. (50

The procedure exposure (total bo residues are descri dose rate on the pa based on the m dimensions of the percentage of the that the relation Popendorf and L

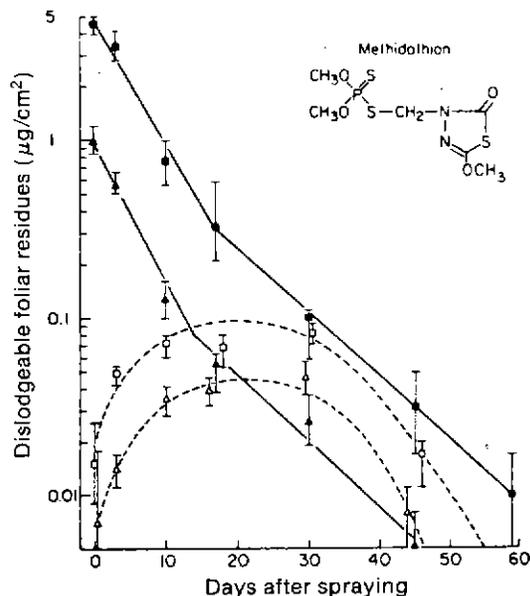


Figure 12. Dissipation curves for dislodgeable foliar residues of methidathion (closed symbols) and methidathion oxon (open symbols) after a Supracide 2E application to orange trees at 5.6 lb AI/100 gal (■, □) and 5.6 lb AI/2250 gal (▲, △) per acre. Vertical lines give the range of values obtained for six field sample replicates. Data from Iwata et al. (56). (Reprinted with permission from American Chemical Society book publications.)

worker exposure to foliar pesticide residues. The data used in this model were obtained from a series of field reentry studies conducted in California with dioxathion, ethyl parathion, and methidathion on grapes, citrus, and peaches. Each pesticide was applied by commercial equipment according to the instructions on the label. Workers equipped with dermal patches were allowed to reenter and harvest fruit on a daily basis from 1 to 3 days after application. Patches were removed after the end of the workday or some fraction of the day and analyzed for pesticide residues according to worker, day, and anatomical site. During each workday, leaf-punch samples were taken in the area of the vineyard or grove being harvested. The leaf samples were collected and analyzed according to the method of Gunther et al. (50).

The procedures used by Pependorf and Leffingwell (44) for calculating the rate of exposure (total body exposure in $\mu\text{g}/\text{h}$) from dermally collected (patches) and extracted residues are described by Davis (59) and Pependorf (60). These procedures extrapolate the dose rate on the patch to that on the skin surrounding each patch. Data were adjusted (61) based on the mensuration formula characteristic of each location and anatomic dimensions of the 50th percentile man (62, 63). Figure 13 presents key skin areas as a percentage of the total surface area (SA). Log-log regression analysis of the data showed that the relation between residues and dose is essentially linear as indicated in Fig. 14. Pependorf and Leffingwell (44) defined the dose to the worker by

$$D' = k_d t R, \quad (2)$$

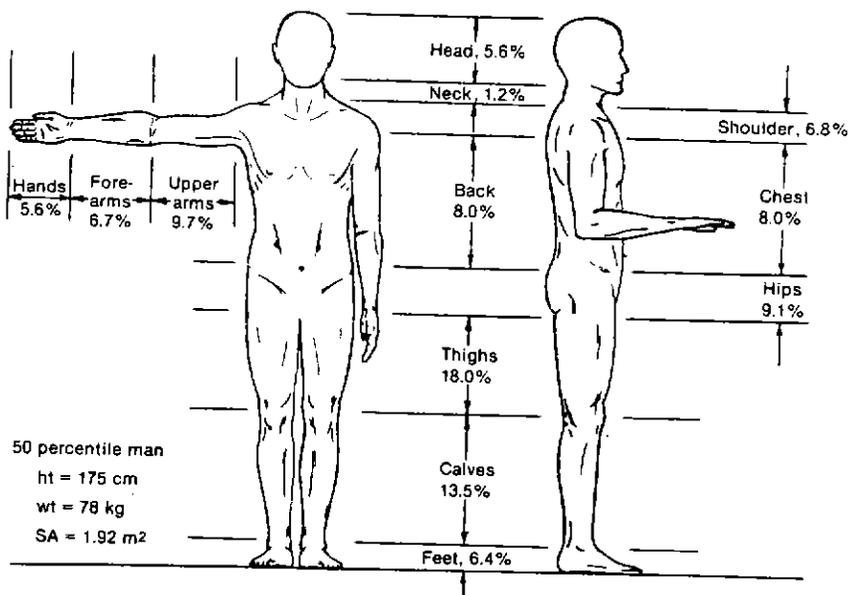


Figure 13. Human dermal surface area model derived from mensuration formula and anatomic dimensions. Each percentage corresponds to the proportion of the total surface area (SA) for each location. Figure taken from Pependorf and Leffingwell (44). (Reprinted with permission from Springer-Verlag, *Residue Reviews*.)

where D' is the dose (in mg), R is the measured residue (in ng/cm^2), t is the occupational exposure time (in h), and k_d is a crop or/and work practice-specific coefficient. The slope of the line (cm^2/h) of k_d value relates a foliar residue (ng/cm^2) to dose rate ($\mu\text{g}/\text{h}$) by simply multiplying a foliar residue level in ng/cm^2 by the k_d value in cm^2/h to give the dose rate in $\mu\text{g}/\text{h}$ for a one-sided leaf residue as shown in Fig. 14. To convert to a two-sided residue all residue values must be divided by 2. A k_d value of 5.1 was the transfer coefficient ($\mu\text{g}/\text{h}$ versus ng/cm^2) most often used by investigators involved in estimating pesticide exposure to workers reentering treated citrus. A k_d value of 5100 is used to relate a dose in $\mu\text{g}/\text{h}$ to a foliar residue in $\mu\text{g}/\text{cm}^2$.

The use of the model developed by Pependorf and Leffingwell (44) to predict harvester exposure to foliar residues in states such as Florida was questioned by Nigg et al. (64) who suggested that differences in California-Florida foliar and soil particulate matter might lead to a 10-fold greater California harvester exposure. This concern prompted these researchers (64) to develop a Florida model for predicting harvester exposure. Chlorobenzilate was applied to a mature block of Valencia oranges. Ten field workers wearing patches entered the grove 2, 3, and 4 days after the pesticide was applied to harvest fruit. Patches were collected at the end of the workday for analysis. All patch data were used in estimating total or partial body exposure ($\mu\text{g}/\text{cm}^2 \cdot \text{h}$). Good correlations were obtained for upper body exposure (excluding hands) versus leaf residues, $R = 0.70$; hand versus leaf residue, $R = 0.97$; lower body versus leaf residue, $R = 0.98$; and total body exposure versus leaf residue, $R = 0.98$.

The predictive equation was Y (estimated total body exposure, $\mu\text{g}/\text{h}$) = (10652

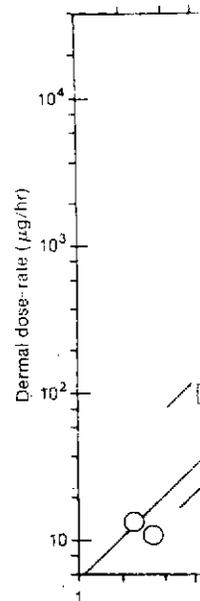


Figure 14. Composite Pependorf et al. (27), and peaches, multiple pesti permission from Spring

$\pm 2393 \text{ cm}^2/\text{h})X + (-$
No log-log transform:
the unmodified Pop
errors in estimating
Pependorf and Leffir
by 2. The results indi
and Florida models.

Nigg et al. (64) su
The Y intercept valu
estimating total body
for a two-sided resid
slope of the regressi

This discussion s
model is based on ch
is based on several
different work condi
environment have
provides some assu
chemicals by envir
sensitive to many of

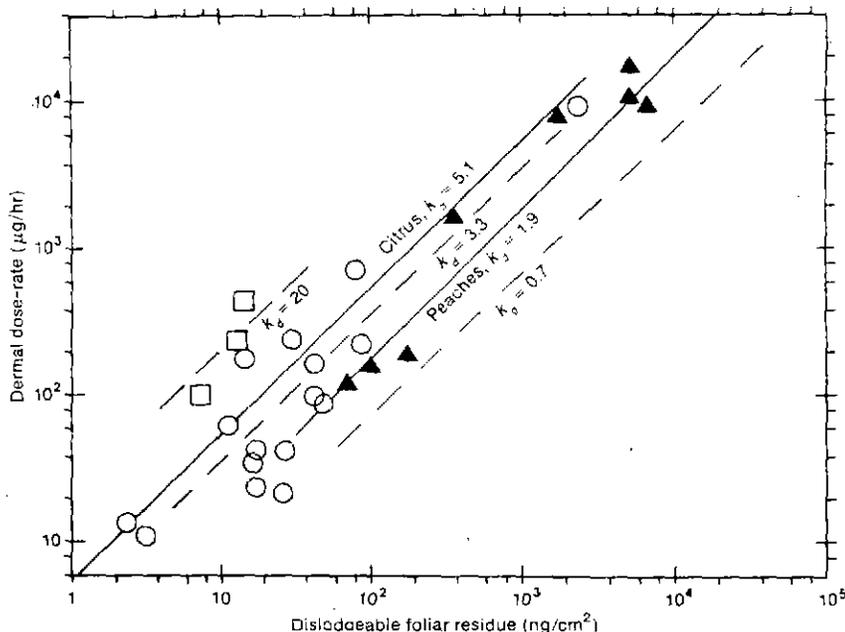


Figure 14. Composite dislodgeable residue versus dermal dose relations from Spear et al. (19), Pependorf et al. (27), and Pependorf (60): \circ , citrus, multiple pesticides; \square , citrus, superoxon; \blacktriangle , peaches, multiple pesticides. Figure taken from Pependorf and Leffingwell (44). (Reprinted with permission from Springer-Verlag, *Residue Reviews*.)

$\pm 2393 \text{ cm}^2/\text{h})X + (-74 \pm 430 \text{ } \mu\text{g}/\text{h})$, where X is the residue on the leaf surface in $\mu\text{g}/\text{cm}^2$. No log-log transformations were required as used in the California model. A reanalysis of the unmodified Pependorf and Leffingwell (44) data by Nigg et al. (64) yielded smaller errors in estimating the dose from the regression line than transformed data. Since Pependorf and Leffingwell (44) used one-sided leaf data in $\mu\text{g}/\text{cm}^2$, their data were divided by 2. The results indicated that there was no significant difference between the California and Florida models.

Nigg et al. (64) suggested that the two models for citrus fruit harvesters be averaged. The Y intercept values are small and should be canceled, leaving a simple equation for estimating total body exposure from foliar residues. This results in the following equation for a two-sided residue: exposure ($\mu\text{g}/\text{h}$) = 10^4 times residue (in $\mu\text{g}/\text{cm}^2$), where 10^4 is the slope of the regression line or transfer coefficient in cm^2/h .

This discussion shows that there are obvious differences in the data base. The Florida model is based on chlorobenzilate, an organochlorine miticide, while the California model is based on several experiments involving organophosphates, different workers, and different work conditions. The results, however, suggest that the differences in the work environment have been overemphasized between California and Florida. This also provides some assurances that estimation procedures used to estimate the uptake of chemicals by environmentally exposed persons are reasonably sturdy and not very sensitive to many of these factors.

5 EARLY AND CONCURRENT PROCEDURES FOR CALCULATING A REENTRY INTERVAL

Simple mathematical equations relating toxic foliar residues and cholinesterase inhibition were desired by regulatory officials to determine reentry intervals. A discussion of the early and concurrent procedures are given in this section.

5.1 Early Procedures

A mathematical procedure was proposed by Serat (65) to utilize organophosphorus pesticide foliar residue and cholinesterase depression data in workers exposed to these residues for estimating reentry times. The dissipation of the organophosphorus pesticide (in $\mu\text{g}/\text{cm}^2$ or ppm) was determined from leaf-punch samples taken at 2, 4, 8, and 28 days after a 7-lb/acre application. Ten workers were allowed to enter the field 3 days after application to harvest oranges for a period of 5 days. Cholinesterase activity was determined in the blood of these workers prior to and during the 5-day work period. Plasma activity was depressed. The residue data taken on each working day reflected the cumulative exposure of the workers. A semilogarithmic plot of ChE activity against cumulative insecticide exposure gave a straight-line relation. If a 10% decrease of ChE is acceptable, the residue producing this effect may be obtained from the curve. A plot of the residue data against time was then used to determine the reentry time.

Serat and Bailey (66) introduced the toxicological potential concept as the ratio between the pesticide residue level on foliage and the dermal LD_{50} value. In a latter study Serat et al. (67) suggested that worker reentry times could be estimated without exposing human beings to pesticide residues. The model combined the toxicological potential (66) concept with the earlier method for calculating safe reentry times (65), but the model neglected the effect of crop on the level of exposure and the toxicity of oxons in the dislodgeable residue.

In an unpublished paper by Spear (68) entitled "The Reentry Problem: Perspectives on the Regulatory Implications of Recent Research," the concept of setting safe pesticide levels on foliage in conjunction with safe reentry intervals was discussed in relation to the presence of ethion and the mono- and dioxons of ethion. The combined hazard of these materials is proportional to the sum of the amounts present weighted by the toxicity of each compound. According to Spear, the difficulties of indirectly estimating the relations between foliar residues, the residues transported to skin (dermal dose), and the absorbed dose leading to a toxic response led the Milby Committee (23) to conclude that "there is no substitute for basing worker safety re-entry intervals on carefully designed studies involving human beings, at least until a sufficient data base and experience permit similar latitude of design of reentry experiments."

Since the time of the report by the Milby Committee and the unpublished report by Spear (68), the relation between exposure, absorption, and the toxic effect has been defined using the results of field studies and animal dermal dose-ChE effect studies. The results of these studies and their usefulness in establishing safe levels and safe reentry times are presented in Sections 5.2 and 6.

5.2 Concurrent Procedures

Popendorf and Leffingwell (44) developed a "uniform field model" for evaluating foliar residue hazards and setting reentry intervals for organophosphorus pesticides. This model

takes into co
reentry (R), th
response (cha

where $k_r = p$
 $T = r$
 $k_d = r$
 $t = e$
 $k_a = \varepsilon$
 $m = t$
 $\Delta\text{AChE} = f$
 $k_e = e$
 $\text{LD}_{50} = d$

In applying t
using eq. (3)

This equatio
sided residue

On the basis
dermal LD_5
be rearrange
shown in Eq

The uniform
new pesticide

takes into consideration the residue initially deposited on foliage (R_0), the residue at reentry (R), the dose (mg) deposited on worker's skin (D'), the absorbed dose (D), and the response (change in AChE). The model is presented in the form of Eq. (3)–(6):

$$R = R_0 \exp(-k_r T) \quad (3)$$

$$D' = k_d t R, \quad (4)$$

$$D = \frac{k_a D'}{m}, \quad (5)$$

$$\Delta\text{AChE} = 1 - \exp\left(\frac{-k_e D}{\text{LD}_{50}}\right), \quad (6)$$

where k_r = pesticide specific residue decay coefficient
 T = reentry interval (days)
 k_d = residue transfer coefficient (cm^2/h)
 t = exposure period (h)
 k_a = absorption coefficient for fraction absorbed
 m = body mass (nominal 70 kg)
 ΔAChE = fraction of RBC cholinesterase inhibited
 k_e = enzyme coefficient (use 6.0 for a topical dose and $k_a = 1$)
 LD_{50} = dermal dose required to kill half the population.

In applying this model, the fractional change in acetylcholinesterase activity is estimated using eq. (3)–(6) or by combining them into Eq. (7):

$$\Delta\text{AChE} = 1 \exp\left[\frac{-k_e k_a \left(\frac{k_d t R_0 \exp(-k_r T)}{m}\right)}{\text{LD}_{50}}\right]. \quad (7)$$

This equation may be simplified further to Eq. (8) for citrus, where $R_0 = 1 \mu\text{g}/\text{cm}^2$ (one-sided residue), $T = 0$, $k_d = 5.0 \text{ cm}^2/\text{h}$, and $t = 8.0 \text{ h}$:

$$\Delta\text{AChE} = 1 - \exp\left(\frac{-3.43}{\text{LD}_{50}}\right). \quad (8)$$

On the basis of Eq. (8), the fractional change in cholinesterase activity is dependent on the dermal LD_{50} of the organophosphorus insecticide under investigation. Equation (7) may be rearranged to determine a reentry interval T for an organophosphorus insecticide as shown in Eq. (9):

$$T = k_r^{-1} \ln \frac{-\text{LD}_{50} \ln(1 - \Delta\text{AChE})}{3.43}. \quad (9)$$

The uniform field model as described above has not been used to set reentry intervals for new pesticides such as chlorthiophos or carbosulfan as carried out in Sections 6.3 and 6.4.

Popendorf and Leffingwell (44) have used this model for calculation reentry intervals for parathion during high oxon production and high-oxon slow-decay conditions. Under conditions of high oxon production, a 35-day reentry interval was calculated for a 2% change in AChE activity. Under conditions of high oxon production and slow-decay rates, a 53-day reentry interval was determined for this change. This model was adjusted by Popendorf and Leffingwell (44) to take into consideration the combined toxicity of the parent pesticides (LD_{50}), their alteration products, and their rates of formation and dissipation (k_r). If the rate of absorption is significantly different for each of the products formed on the surface of the leaf, individual absorption rates may need to be determined for the pesticide and each alteration product. The Popendorf and Leffingwell (44) unified field model is conceptually sound but requires the development of enzyme, absorption, residue transfer, and residue decay coefficients in conjunction with dermal toxicity data and residue data to set reentry intervals. In the development of this model many of the parameters were estimated from a number of studies conducted with organophosphorus pesticides.

6 MATHEMATICS OF SETTING SAFE LEVELS ON FOLIAGE

Current mathematical procedures developed in California and used by the California Department of Food and Agriculture are described in this section along with procedures recommended by the U.S. Environmental Protection Agency (12).

6.1 Dermal Dose-ChE Response Studies and Field Worker Observations

The results of dermal dose-ChE response studies were used in conjunction with the results of field worker studies for estimating safe foliar residue levels for a number of

TABLE 4. Dermal Dose-ChE Response Expressed in Terms of Total Body Surface, Body Weight, and Safety Index

| Pesticides | ED ₅₀ ($\mu\text{g}/\text{cm}^2$ of body surface) ^a | ED ₅₀ (mg/kg) ^b | Dermal LD ₅₀ (mg/kg) | Safety Index LD ₅₀ /ED ₅₀ (mg/kg) |
|----------------|---|---------------------------------------|------------------------------------|--|
| Paraoxon | 0.33 ± 0.2 | 0.5 | 2.0 ^c | 4.0 |
| Parathion | 2.4 ± 0.3 | 3.4 | 21.0 ^d | 6.2 |
| Methidathion | 10.0 ± 0.3 | 15.0 | 150.0 ^e | 10.0 |
| Dialifor | 23.0 ± 0.3 | 33.0 | — | — |
| Azinphosmethyl | 25.0 ± 0.5 | 35.0 | 220.0 ^d | 6.3 |
| Phosalone | 188.0 ± 0.4 | 265.0 | 1450.0 ^f | 5.5 |
| Dimethoate | 432.0 ± 2 | 611.0 | 1420.0 ^g | 2.3 |

^aPesticides were individually applied in 1.0 mL of acetone to the clipped backs (25 cm²) of 220–240-g male rats. Blood was taken 72 h after application for ChE determination. Response expressed in terms of total body surface (325 cm²) from dermal dose-ChE response curves in Figs. 2 and 3. Values are given with 95% confidence limits.

^bValues determined from dermal dose-ChE response curves.

^cEstimated.

^dGaines (40).

^eCIBA-GEIGY Toxicology Data Bulletin.

^fMazuret (49).

^gGaines (41).

Source: Knaak et al. (42).

TABLE 5. I
Dose-ChE I

Pesticides^a

Paraoxon

Methidathion

Azinphosme

Methidathion

Dialifor

Parathion

Phosalone

Azinphosme

Dimethoate

^aPesticide s

^bED₅₀ of pu

^cRelative to

^dSpear et al

^eEstimated

^fPopendorf

^gRichards e

Source: Tab

organopho

data (ED₅₀

of body w

cell inhibi

for parao

thoate. In

Richards

estimate

azinphosr

0.02 $\mu\text{g}/\text{cr}$

standards

oxon, dia

Table 4. I

and the p

pesticide

safe le

=

6.2 Rec

The oxid

to oxons

for the c

methidat

TABLE 5. Establishment of Safe Levels ($\mu\text{g}/\text{cm}^2$) on Tree Foliage Using Results of Dermal Dose-ChE Response Studies in Male Rats and Field Reentry Studies

| Pesticides ^a | Slopes | ED ₅₀ ($\mu\text{g}/\text{cm}^2$ of body surface) | Relative Toxicity ^b | Safe Level on Foliage ($\mu\text{g}/\text{cm}^2$) ^f |
|---------------------------|--------|---|--------------------------------|--|
| <i>Paraoxon</i> | 2.3 | 0.33 | 1.0 | 0.02 ^d |
| Methidathion | 2.9 | 10.00 | 30.0 | 0.60 |
| <i>Azinphosmethyloxon</i> | 2.0 | 0.82 | 1.0 | 0.05 ^e |
| Methidathionoxon | 1.8 | 2.2 | 3.0 | 0.15 |
| Dialifor | 1.3 | 23.0 | 0.12 | 0.8 |
| Parathion | 1.3 | 2.4 | 0.013 | 0.09 |
| <i>Phosalone</i> | 1.5 | 188.0 | 1.0 | 7.0 ^f |
| <i>Azinphosmethyl</i> | 0.9 | 25.0 | 1.0 | 3.1 ^g |
| Dimethoate | 0.7 | 432.0 | 17.0 | 53.0 |

^aPesticide standard in italic.

^bED₅₀ of pesticide under investigation divided by ED₅₀ of pesticide standard.

^cRelative toxicity multiplied by safe level of standard.

^dSpear et al. (69).

^eEstimated.

^fPopendorf et al. (27).

^gRichards et al. (70).

Source: Table is composite of data from Knaak et al. (42) and Knaak and Iwata (71).

organophosphorus and carbamate pesticides. Table 4 gives the dermal dose-ChE response data (ED₅₀) in terms of body weight and total body surface, and the dermal LD₅₀ in terms of body weight. On the basis of total body surface, the quantities producing 50% red blood cell inhibition were 0.33, 2.4, 10.0, 23.0, 25.0, 188.0, and 432.0 $\mu\text{g}/\text{cm}^2$ of skin, respectively, for paraoxon, parathion, methidathion, dialifor, azinphosmethyl, phosalone, and dimethoate. In Table 5, these values and the results of studies conducted by Spear et al. (69), Richards et al. (70), and Popendorf et al. (27) were used by Knaak et al. (42, 43, 71) to estimate safe levels on foliage. The field exposure studies established safe levels for azinphosmethyl, azinphosmethyl oxon, phosalone, and paraoxon of 3.1, 0.05, 7.0, and 0.02 $\mu\text{g}/\text{cm}^2$, respectively. These pesticides and their safe foliar levels were used as standards for establishing additional safe levels on foliage for methidathion, methidathion oxon, dialifor, parathion, and dimethoate using their relative toxicities as shown in Table 4. In practice this was accomplished by grouping the pesticides under investigation and the pesticide standards according to their slopes, and determining a safe level for the pesticide under investigation using Eq. (10):

$$\begin{aligned} &\text{safe level } (\mu\text{g}/\text{cm}^2) \text{ for pesticide under investigation} \\ &= \text{safe level of standard} \times \text{ED}_{50} (\mu\text{g}/\text{cm}^2) \text{ of pesticide} \div \text{ED}_{50} \text{ of standard.} \quad (10) \end{aligned}$$

6.2 Reentry Intervals for Thions and Oxons

The oxidative conversion of methidathion, azinphosmethyl, and parathion on leaf surfaces to oxons necessitated the development of a procedure for establishing safe levels on foliage for the combined hazard posed by thion and oxon residues. This was accomplished for methidathion, azinphosmethyl, and parathion (71) by allowing the oxon to be present at a

TABLE 6. Procedure for Establishing Safe Levels ($\mu\text{g}/\text{cm}^2$) for Thions + Oxons on Tree Foliage

| Application to Citrus ^a | Days Elapsed ^a | Thion ^a | Oxon ^b | Thion + Oxon | Thion + Oxon \times RT ^c | Thion + Oxon \times RT \times SL ^d for Thion |
|------------------------------------|---------------------------|--------------------|-------------------|--------------|---------------------------------------|---|
| Parathion | 10 | 0.35 | 0.02 | 0.37 | 0.49 | 0.07 |
| 10 lb AI/1600 gal per acre | 20 | 0.09 | 0.01 | 0.10 | 0.16 | 0.06 ^e |
| Methidathion | 10 | 1.0 | 0.08 | 1.08 | 1.38 | 0.4 |
| 5.6 lb AI/100 gal per acre | 20 | 0.25 | 0.1 | 0.35 | 0.73 | 0.3 |
| | 30 | 0.11 | 0.08 | 0.19 | 0.50 | 0.2 ^e |
| Azinphosmethyl | 10 | 1.5 | 0.05 | 1.55 | 2.91 | 1.7 |
| 6.0 lb AI/1200 gal per acre | 20 | 1.3 | 0.05 | 1.35 | 2.86 | 1.6 ^e |
| | 30 | 1.1 | 0.05 | 1.15 | 2.51 | 1.5 |

^aTaken from Fig. 10, 11, and 12.

^bOxons must be at safe level indicated in Table 2. Method assumes oxons will be at a safe level when safe level for thion + oxon is reached.

^cRT = relative toxicity from Table 2 (ED₅₀ of thion \div ED₅₀ of oxon).

^dSL = safe levels for thions from Table 2.

^eSafe levels for thion + oxon.

Source: Knaak and Iwata (71).

HAZAR
DISSEMINABLE FOLIAR RESIDUES ($\mu\text{g}/\text{cm}^2$)

Figure 15. Dissipation trees. —■—, 10 lb AI paraoxon is safe level for thion + oxon (71). (Reprinted with p

safe level and by re 1.6 $\mu\text{g}/\text{cm}^2$, respectively safe level for the mixture of thion + oxon and thion mix

ED₅₀ (m

where P_1 and P_2 are or 30 days as shown the mixture was 23 determined by Eq. 1 paraoxon, 10 days

SL. r

The relation between safe level for total

6.3 Reentry Int

These studies by determining a ree

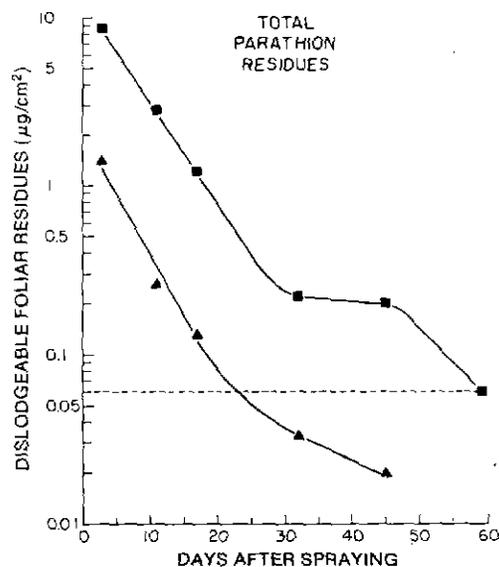


Figure 15. Dissipation of combined residues (thion + oxon) of parathion and paraoxon on orange trees. —■—, 10 lb AI parathion/100 gal per acre; —▲—, 10 lb AI parathion/1600 gal per acre. Dashed line is safe level for thion + oxon. Curves are drawn from Fig. 10. Figure taken from Knaak and Iwata (71). (Reprinted with permission from American Chemical Society book publications.)

safe level and by reducing the combined residue of oxon and thion to 0.06, 0.02, and 1.6 $\mu\text{g}/\text{cm}^2$, respectively, for parathion, methidathion, and azinphosmethyl; see Table 6. A safe level for the mixture may also be estimated by determining the toxicity (ED_{50}) of the oxon and thion mixture using the method of Finney (72) in Eq. (11):

$$\text{ED}_{50} (\text{mixture}, \mu\text{g}/\text{cm}^2) = \left[\frac{P_1}{\text{ED}_{50,1}} + \frac{P_2}{\text{ED}_{50,2}} + \dots + \frac{P_N}{\text{ED}_{50,N}} \right]^{-1}, \quad (11)$$

where P_1 and P_2 are the proportions of oxon and thion, respectively, on foliage after 10, 20, or 30 days as shown in Table 6. In the case of parathion–paraoxon at 10 days, the ED_{50} of the mixture was 23.4 $\mu\text{g}/\text{cm}^2$, while the safe level for the mixture was 0.067 $\mu\text{g}/\text{cm}^2$ as determined by Eq. (12). This value is equivalent to the one given in Table 5 for parathion–paraoxon, 10 days after application.

$$\text{SL, mixture} (\mu\text{g}/\text{cm}^2) = \frac{\text{ED}_{50, \text{thion + oxon}}}{\text{ED}_{50, \text{phosalone}}} \times \text{SL, phosalone}. \quad (12)$$

The relation between total parathion–paraoxon residues, their rate of dissipation, and the safe level for total thion and oxon is shown in Fig. 15. The dashed line is the safe level.

6.3 Reentry Interval for Chlorthiophos

These studies by Knaak et al. (42) and Knaak and Iwata (71) provided a method for determining a reentry interval for a new pesticide, chlorthiophos, on citrus. Figure 16

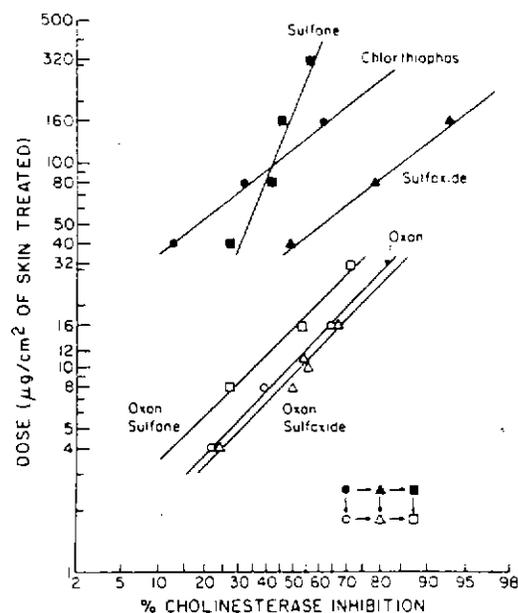


Figure 18. Percentage of red blood cell ChE inhibition in rats sacrificed 72 h after treatment of nature of skin surface with chlorthiophos or one of its five oxidation products. Figure taken from Iwata et al. (73). (Reprinted with permission from American Chemical Society, *Journal of Agriculture, Food and Chemistry*.)

(Iwata et al., 73) shows the dislodgeable residue data obtained when a commercial formulation of chlorthiophos, Celathion 40 W, is applied to citrus at a rate of 9.5 lb AI/1900 gal per acre. The chemical structures of the dislodgeable residues are given in Fig. 17. Chlorthiophos and five toxic oxidation products were found. Dermal dose-ChE response studies in the rat were performed on each toxicant to determine its ED_{50} value as shown in Fig. 18. The oxons were similar in their toxicity, while chlorthiophos, chlorthiophos sulfoxide, and chlorthiophos sulfone were less toxic. Safe levels on foliage were determined for each toxicant using the procedure of Knaak et al. (42). Paraoxon, parathion, and azinphosmethyl were used as pesticide standards (Table 7).

Two procedures were used to calculate safe reentry levels for chlorthiophos and its oxidation products on citrus. The first method used the procedure of Knaak and Iwata (71) for the combined thion and oxon residues as shown in Table 8. This method may be simplified using Eq. (11) and (12). Equation (11) first determines the ED_{50} of the mixture (thions and oxons). The value ($15.1 \mu\text{g}/\text{cm}^2$, 20 days after spraying) was used in Eq. 12, where it was divided by the ED_{50} of the oxon sulfoxide ($40.3 \mu\text{g}/\text{cm}^2$) and multiplied by the safe level (SL) for chlorthiophos sulfoxide ($0.19 \mu\text{g}/\text{cm}^2$) to give $0.07 \mu\text{g}/\text{cm}^2$ as the safe level for the combined foliar residues in Table 8.

The second procedure (Iwata et al., 73) used to determine a safe reentry level was a modification of one proposed by the U.S. Environmental Protection Agency (12); see Table 9. A no observable effect level (NOEL) was determined (ED_{10}) for the combined residues of chlorthiophos sulfone and sulfoxide, and chlorthiophos oxon sulfoxide and

TABLE 7. Establishment of Safe Residue Levels ($\mu\text{g}/\text{cm}^2$) on Citrus Tree Foliage Using Results of Dermal Dose-ChE Response Curves and Field Reentry Studies according to Knaak et al. (42)

| Insecticide or Alteration Product ^a | Slope of Dose-Response Curve ^b | ED ₅₀ ($\mu\text{g}/\text{cm}^2$) of total body surface ^c | Relative Toxicity ^d | Safe Level on Foliage, ($\mu\text{g}/\text{cm}^2$) ^e |
|--|---|---|--------------------------------|---|
| Chlorthiophos sulfoxide | 2.5 | 3.1 | 9.4 | 0.19 |
| Chlorthiophos | 2.4 | 8.8 | 27 | 0.54 |
| <i>Paraoxon</i> | 2.3 | 0.33 | 1 | 0.02 ^f |
| Chlorthiophos oxon sulfone | 2.0 | 1.2 | 3.6 | 0.07 |
| Chlorthiophos oxon sulfoxide | 1.9 | 0.69 | 0.29 | 0.03 |
| <i>Parathion</i> | 1.3 | 2.4 | 1 | 0.09 ^f |
| <i>Azinphosmethyl</i> | 0.9 | 25 | 1 | 3.0 ^g |
| Chlorthiophos sulfone | 0.8 | 13 | 0.53 | 1.6 |

^aReference compound is in italics; this compound is one for which actual field safety information is available.

^bSlopes derived from Fig. 18 for chlorthiophos and its alteration products. Data used to construct the figure were statistically analyzed according to the log-probit analysis procedure of Finney (72).

^cED₅₀ in $\mu\text{g}/\text{cm}^2$ multiplied by 25 cm² (treated area) and divided by 325 cm² (total surface area of the rat).

^dED₅₀ of the compound under investigation divided by the ED₅₀ of the reference compound.

^eRelative toxicity multiplied by the established safe level of the reference as determined by actual reentry studies.

^fSpear et al. (69).

^gRichards et al. (70).

Source: Iwata et al. (73).

TABLE 8. Procedure for Establishing Safe Levels ($\mu\text{g}/\text{cm}^2$) of Total Thions Plus Oxons of Chlorthiophos on Citrus Tree Foliage According to Knaak and Iwata (71)

| Days After Spraying | Residues ($\mu\text{g}/\text{cm}^2$) | | | Thion + Oxon \times RT ^c | $\frac{(\text{Thion} + \text{Oxon})}{(\text{Thion} + \text{Oxon} \times \text{RT})} \times \text{SL}$ for Thion ^d ($\mu\text{g}/\text{cm}^2$) |
|---------------------|--|-------------------|--------------|---------------------------------------|--|
| | Thion ^a | Oxon ^b | Thion + Oxon | | |
| 20 | 0.12 | 0.11 | 0.23 | 0.60 | 0.07 |
| 40 | 0.04 | 0.09 | 0.13 | 0.43 | 0.06 |
| 60 | 0.04 | 0.07 | 0.11 | 0.37 | 0.06 |

^aSince no chlorthiophos is present at or after 20 days, thion residues are the sum of chlorthiophos sulfoxide and sulfone. Values were obtained from Fig. 16.

^bSince no chlorthiophos oxon is present at or after 20 days, oxon residues are the sum of chlorthiophos oxon sulfoxide and sulfone. Values were obtained from Fig. 16.

^cRT (relative toxicity) is the ED₅₀ of the chlorthiophos sulfoxide divided by the ED₅₀ of the oxon sulfoxide. This RT differs in definition from that in Table 7.

^dSL (safe level) for the thion is 0.19 $\mu\text{g}/\text{cm}^2$ as given in Table 7 for the most toxic thion, chlorthiophos sulfoxide.

Source: Iwata et al. (73).

TABLE 9. Calculations and Modifications^a

| Day | Co |
|-----|----|
| 20 | 2 |
| 40 | 2 |
| 60 | 2 |

^aThe modification is the ratio of total toxic residue to the total residue. This is the ratio of Fig. 16.

^bNo effect level (NOEL) = (25 cm²)/(0.23 kg/d).

^cP = proportion of total dose.

^dED₁₀ for chlorthiophos: 35, 12, 4, 2, 2, and 2.

^eAllowable exposure = (AEL) / (P).

^fTotal dose = (AEL) / (P).

^gFrom total dose = (AEL) / (P).

^hdislodgeable foliar residue (DFR).

ⁱEnvironmental Protection Agency (EPA).

^jSource: Iwata et al. (73).

sulfone on foliage dose-ChE response curves determined using Eq. (14), while

ED₁₀(mixture)

NOEL (mixture)

AEL (mixture)

A total dose was determined. The level was determined by the determined grape dose ($\mu\text{g}/\text{h}$) to dis-

TABLE 9. Calculation of Reentry Intervals According to U.S. EPA Guidelines (12) with Slight Modifications^a

| Day | Compound Ratio ^b | NOEL ^c ($\mu\text{g}/\text{kg}\cdot\text{day}$) | AEL ^d ($\mu\text{g}/\text{kg}\cdot\text{day}$) | Total Dose ^e ($\mu\text{g}/\text{h}$) | Reentry Level ^f ($\mu\text{g}/\text{cm}^2$) |
|-----|-----------------------------|---|--|---|---|
| 20 | 4:1:1:3 | 391 | 39.1 | 342 | 0.08 |
| 40 | 2:1:2:4 | 304 | 30.4 | 266 | 0.06 |
| 60 | 2:1:2:3 | 309 | 30.9 | 270 | 0.06 |

^aThe modification involves taking into account all toxic residues present on the foliage and using a total toxic residue level curve.

^bThis is the ratio of sulfoxide:sulfone:oxon sulfoxide:oxon sulfone present on foliage as shown in Fig. 16.

^cNo effect level (NOEL) calculated from data from dermal dose-ChE response curve. $\text{NOEL} = \text{ED}_{10} (25 \text{ cm}^2)/(0.23 \text{ kg}/\text{day})$. Predicted $\text{ED}_{10} = [P_1/\text{ED}_{10,1} + P_2/\text{ED}_{10,2} + \dots + P_N/\text{ED}_{10,N}]^{-1}$, where P = proportion of component in mixture (Finney, 72). ED_{10} values were extrapolated from Fig. 18. ED_{10} for chlorthiophos, its sulfoxide, its sulfone, its oxon, its oxon sulfoxide, and its oxon sulfone were 35, 12, 4, 2, 2, and 3.5 $\mu\text{g}/\text{cm}^2$, respectively.

^dAllowable exposure level (AEL) = NOEL/SF . Safety factor (SF) = 10.

^eTotal dose = (AEL)(body weight, 70 kg)/(duration, 8 h/day).

^fFrom total dose determine reentry level from graph of whole-body dermal dose ($\mu\text{g}/\text{h}$) versus dislodgeable foliar residues (ng/cm^2) from data of Popendorf (60) as abbreviated by U.S. Environmental Protection Agency (12).

Source: Iwata et al. (73).

sulfone on foliage, 20, 40, and 60 days after spraying. The ED_{10} values from the dermal dose-ChE response curves (Fig. 18) were used. The ED_{10} value for the mixture was determined using Eq. (13). The NOEL was calculated using the ED_{10} value for the mixture in Eq. (14), while an acceptable exposure level (AEL) was determined by Eq. (15).

$$\text{ED}_{10}(\text{mixture}, \mu\text{g}/\text{cm}^2) = \left[\frac{P_1}{\text{ED}_{10,1}} + \frac{P_2}{\text{ED}_{10,2}} + \dots + \frac{P_N}{\text{ED}_{10,N}} \right]^{-1}, \quad (13)$$

$$\text{NOEL} (\mu\text{g}/\text{kg}\cdot\text{day}) = \frac{\text{ED}_{10} (25 \text{ cm}^2)}{0.23 \text{ kg}/\text{day}}, \quad (14)$$

$$\text{AEL} (\mu\text{g}/\text{kg}\cdot\text{day}) = \frac{\text{NOEL}}{\text{SF}}, \quad (15)$$

$$\text{total dose} = (\text{AEL})(\text{body weight}, 70 \text{ kg})(\text{duration}, 8 \text{ h}/\text{day}). \quad (16)$$

A total dose was calculated using the AEL value in Eq. (16). Finally, in Eq. (17), a reentry level was determined by dividing the total dose by a transfer coefficient $k_d = 5.1$, determined graphically by Popendorf and Leffingwell (44) relating whole body dermal dose ($\mu\text{g}/\text{h}$) to dislodgeable foliar residues (ng/cm^2):

$$\text{reentry level} (\text{ng}/\text{cm}^2) = \frac{\text{total dose} (\mu\text{g}/\text{h})}{k_d = 5.1 \text{ cm}^2/\text{h}}. \quad (17)$$

The reentry or safe levels determined by these two procedures gave almost equivalent values because the same dislodgeable residue and toxicological data base were used. Differences, however, exist in the manner in which these two methods used exposure data. In the first method, results of worker exposure studies were used to estimate safe residue levels for certain pesticides in the field using dislodgeable residue data and red blood cell cholinesterase measurements in the worker. The safe level for the pesticide was then used as a field standard in conjunction with relative animal potency data to relate the safe level of the standard to a pesticide under investigation. The second procedure did not use cholinesterase values from exposed workers, but rather developed a graph relating foliar residues ($\mu\text{g}/\text{cm}^2$) to dose ($\mu\text{g}/\text{h}$) for workers harvesting crops. Animal dermal dose-ChE response data were used to determine an acceptable AEL, total dose, and safe level from the graph.

Either method is acceptable for setting reentry intervals for organophosphorus pesticides. However, the Knaak and Iwata (71) method required field observations relating residue on foliage to changes in field worker cholinesterase values for the pesticide standard. Blood cholinesterase measurements in field workers are not required by the modification of the U.S. EPA procedure (12). In either case, workers should be monitored for AChE inhibition after a reentry interval is established on a new organophosphorus pesticide. On the basis of the calculated safe reentry levels determined for chlordiophos, a 70-day reentry interval was proposed by Iwata et al. (73). Because of this long reentry interval and the marginal efficacy of this organophosphate, Celathion 40 W has not been registered in California.

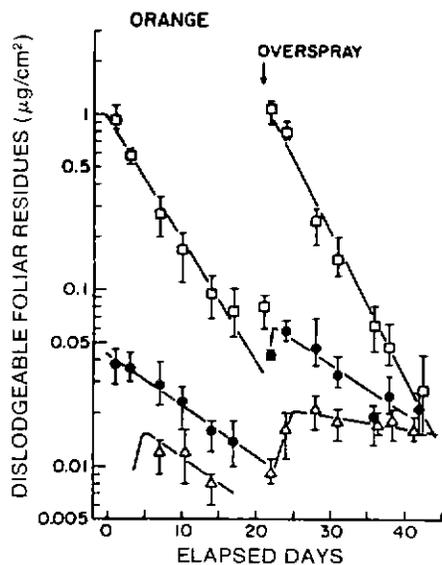


Figure 19. Dislodgeable foliar residues of carbosulfan (\square), carbofuran (\bullet), and 3-hydroxycarbofuran (\triangle) after treatment of orange trees with Advantage 2.5EC insecticide formulation at 1.5 lb AI/200 gal per acre. Each datum point is the mean value obtained from six replicate field samples, and the vertical lines show the range of values found. Figure taken from Iwata et al. (74). (Reprinted with permission from American Chemical Society, *Journal of Agriculture, Food and Chemistry*.)

6.4 Reentry In

The procedure us recently used by I insecticide contain mature orange tre given in Fig. 19 w to carbofuran an by Iwata et al. (74 chlordiophos in

Figure 20 give the rat. Safe levels actual field infori furan were all fou levels varied from via the dermal ro determine safe lev

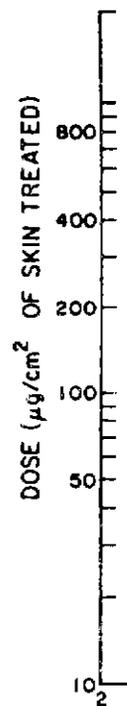


Figure 20. Percenta of skin surface with residues versus dose (74). (Reprinted with permission from American Chemical Society, *Journal of Agriculture, Food and Chemistry*.)

6.4 Reentry Interval for Carbosulfan

The procedure used to determine a safe level and reentry period for chlordiophos was recently used by Iwata et al. (74) to establish a reentry interval for Advantage 2.5EC, a new insecticide containing carbosulfan as the active ingredient. This insecticide was applied to mature orange trees at a rate of 1.5 lb AI/200 gal per acre. Foliar dislodgeable residue data given in Fig. 19 were obtained over a period of 45 days. Carbosulfan is degraded on foliage to carbofuran and a metabolite, 3-hydroxycarbofuran. A safe reentry level was determined by Iwata et al. (74) for total residues of carbosulfan on oranges using the procedure used for chlordiophos in Section 6.3.

Figure 20 gives the dermal dose-ChE response curves obtained for these products in the rat. Safe levels were determined using parathion as the reference standard for which actual field information was available. Carbosulfan, carbofuran, and 3-hydroxycarbofuran were all found to be less dermally toxic than parathion, as shown in Table 10. Safe levels varied from 0.3 to 1.3 $\mu\text{g}/\text{cm}^2$ with carbosulfan and carbofuran being equally toxic via the dermal route. In Table 11 the procedure of Knaak and Iwata (71) was used to determine safe levels for the total carbamate residues of carbofuran on citrus foliage.

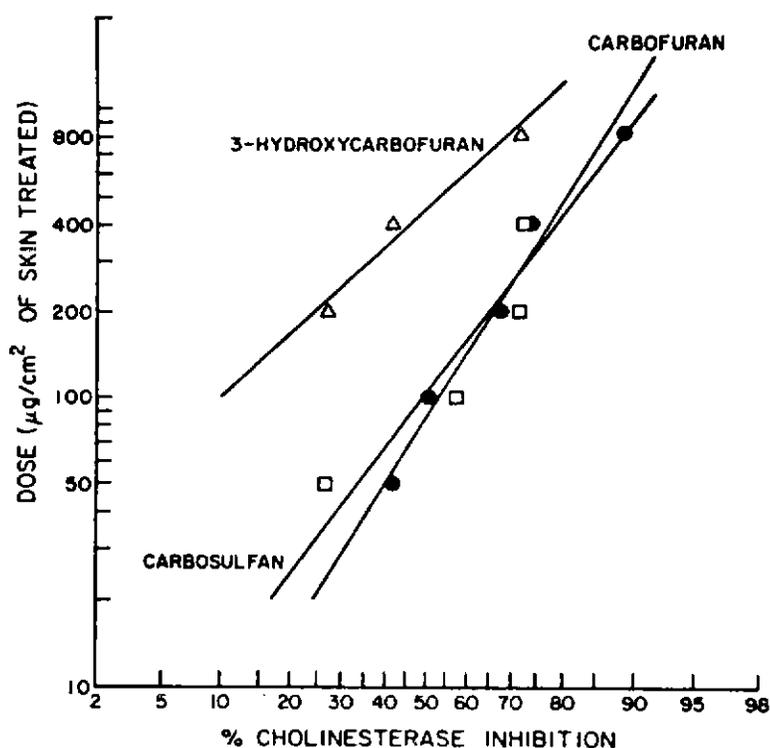


Figure 20. Percentage of red blood cell ChE inhibition in rats sacrificed 24 h after treatment of 25 cm^2 of skin surface with carbosulfan, carbofuran, or 3-hydroxycarbofuran. Figure taken from Iwata et al. (74). (Reprinted with permission from American Chemical Society. *Journal of Agriculture, Food and Chemistry*.)

TABLE 10. Calculation of Safe Residue Levels ($\mu\text{g}/\text{cm}^2$) on Citrus Tree Foliage Using Results of Dermal Dose-*ChE* Response Curves and Field Reentry Studies According to Knaak et al. (42)

| Insecticide or Alteration Product | Slope of Dose-Response Curve ^a | ED ₅₀ ($\mu\text{g}/\text{cm}^2$ of total body surface) ^b | Relative Toxicity ^c | Safe Level on Foliage ($\mu\text{g}/\text{cm}^2$) ^d |
|-----------------------------------|---|--|--------------------------------|--|
| Carbofuran | 1.12 | 6.6 ± 0.4 | 2.8 | 0.3 |
| Carbosulfan | 1.35 | 7.8 ± 0.4 | 3.3 | 0.3 |
| 3-Hydroxy carbofuran | 1.95 | 34.4 ± 0.3 | 14.3 | 1.3 |
| Parathion | 1.3 | 2.4 ± 0.3 | 1.0 | 0.09 ^e |

^aValues for the three carbamate compounds were calculated from the data used to construct Fig. 19. Data were subjected to the log-probit analysis procedure of Finney (72).

^bED₅₀ in $\mu\text{g}/\text{cm}^2$ multiplied by 25 cm^2 (treated area) and divided by 325 cm^2 (total surface area of the rat).

^cED₅₀ of the compound under investigation divided by the ED₅₀ of parathion, a reference compound for which actual field safety information is available.

^dRelative toxicity multiplied by the established safe level of parathion, which was determined by actual reentry studies.

^eSpear et al. (69).

Source: Iwata et al. (74).

Equations (11) and (12) may also be used to calculate a safe level for the mixture (total carbamates). In Eq. (12), the ED₅₀ of the mixture (1, 3, 7, and 10 days after spraying) was divided by the ED₅₀ of parathion and multiplied by the safe level determined in Table 10 for carbofuran (0.3 $\mu\text{g}/\text{cm}^2$). The small differences in the dermal ED₅₀ values of carbosulfan (101 $\mu\text{g}/\text{cm}^2$) and carbofuran (86 $\mu\text{g}/\text{cm}^2$) and the small quantities of 3-hydroxycarbofuran formed on foliage resulted in safe levels for the mixture equivalent to carbosulfan or carbofuran.

Somewhat lower reentry levels were obtained in Table 12 when the reentry levels were calculated using the modified U.S. Environmental Protection Agency guidelines (12) as described in Section 6.3 for chlorthiophos. The lower values are probably a result of using the ED₁₀ values in place of the ED₅₀ values for the mixture of carbamates and the transfer coefficient of 5.1 (k_r for citrus). On the basis of these results and the dislodgeable residue data, a 7-day reentry time was selected as being sufficient to protect the health of workers.

Nigg et al. (75) conducted a similar study in Florida using carbosulfan. In experiment 1, Advantage 2.5EC was applied twice during the summer at the rate of 4 lb AI/750 gal per acre to mature Valencia oranges. A similar spray program, experiment 2, was conducted by Nigg et al. (75) in Florida using a 1-lb rate. Carbofuran was the principal metabolite present on foliage.

Reentry intervals for the 4- and 1-lb AI/acre application rates in experiments 1 and 2 were calculated according to each of the two procedures used by Iwata et al. (74). The ED₁₀ and ED₅₀ values determined by Iwata et al. (74) for carbosulfan and carbofuran from dermal dose-*ChE* response studies were used in conjunction with dislodgeable residue data from experiments 1 and 2 to determine a safe reentry period for total carbamate residues using the procedure of Knaak and Iwata (71) in Table 13 and the modified U.S. Environmental Protection Agency method (12) in Table 14. This table indicates that safe reentry levels are reached in these experiments on days 2 and 3. The California-Florida citrus studies (Iwata et al., 74; Nigg et al., 75) with carbofuran were the first studies to

TABLE 11. Calculation of Safe Levels ($\mu\text{g}/\text{cm}^2$) Based on Total Carbamate Residues of Carbosulfan on Citrus Tree Foliage

| Days After Spraying | Distodgeable Foliar Residues ($\mu\text{g}/\text{cm}^2$) ^a | | | Total Carbamate (A) | Toxic Equivalents, (CS + CF) + (HCF \times RT) ^b (B) | Safe Level for CS + CF + HCF Mixture, (A/B) \times SL for CF ($\mu\text{g}/\text{cm}^2$) ^c |
|---------------------|---|-----------------|---------------------------|---------------------|---|---|
| | Carbosulfan (CS) | Carbofuran (CF) | 3-Hydroxycarbofuran (HCF) | | | |
| 1 | 0.94 | 0.038 | <0.01 | 0.99 | 0.98 | 0.30 |
| 3 | 0.58 | 0.036 | <0.01 | 0.63 | 0.62 | 0.30 |
| 7 | 0.27 | 0.029 | 0.012 | 0.31 | 0.30 | 0.31 |
| 10 | 0.17 | 0.023 | 0.012 | 0.21 | 0.19 | 0.32 |

^aValues are those used to construct Fig. 19.

^bRT (relative toxicity) is the ED_{50} of CS divided by the ED_{50} of HCF. This RT differs in definition from that given in Table 10.

^cSL (safe level) is $0.3 \mu\text{g}/\text{cm}^2$ as found for CF (Table 10), the most dermally toxic of the three carbamate compounds.

Source: Iwata et al. (74).

TABLE 12. Calculation of Reentry Intervals According to U.S. Environmental Protection Agency (12) Guidelines with Slight Modification^a

| Days After Spraying | Compound Ratio ^b CS:CF:HCF | NOEL ^c ($\mu\text{g}/\text{kg}\cdot\text{day}$) | AEL ^d ($\mu\text{g}/\text{kg}\cdot\text{day}$) | Total Dose ^e ($\mu\text{g}/\text{h}$) | Reentry Level ^f ($\mu\text{g}/\text{cm}^2$) |
|---------------------|--|---|--|---|---|
| 1 | 94:3.8:1 | 1224 | 122 | 1068 | 0.21 |
| 3 | 58:3.6:1 | 1209 | 121 | 1059 | 0.21 |
| 7 | 22.5:2.4:1 | 1197 | 120 | 1050 | 0.21 |
| 10 | 14.2:1.9:1 | 1200 | 120 | 1050 | 0.21 |

^aModification involves taking into account all toxic residues present on the foliage and using a total toxic residue curve.

^bRatios calculated from values used to construct Fig. 19.

^cNo effect level (NOEL) calculated from data from dermal dose-ChE response curve. $\text{NOEL} = \text{ED}_{10}(25 \text{ cm}^2)/(0.23 \text{ kg}\cdot\text{day})$. Predicted $\text{ED}_{10} = [P_1/\text{ED}_{10,1} + P_2/\text{ED}_{10,2} + \dots + P_N/\text{ED}_{10,N}]^{-1}$, where P = proportion of component in mixture (Finney, 72). ED_{10} values were extrapolated from Fig. 19. ED_{10} values for CS, CF, and HCF were 11.5, 6.24, and 98.8 $\mu\text{g}/\text{cm}^2$, respectively.

^dAllowable exposure level (AEL) = NOEL/SF . Safety factor (SF) = 10.

^eTotal dose = (AEL)(body weight, 70 kg)/(duration, 8 h/day).

^fFrom total dose, reentry level was determined from the graph of whole-body dermal dose ($\mu\text{g}/\text{h}$) versus dislodgeable foliar residues (ng/cm^2) from the data of Pependorf and Lellingwell (44). Total dose was divided by 5.1, the k_d for citrus; derivation was based on the area of only one side of the leaf.

Source: Iwata et al. (74).

TABLE 13. Reentry Levels and Intervals for Total Carbamate Residues on Leaves

| Days After Spraying | Dislodgeable Foliar Residues ($\mu\text{g}/\text{cm}^2$) ^a | | | Reentry Level ($\mu\text{g}/\text{cm}^2$ total carbamates) ^b |
|---------------------|--|-----------------|----------------------------|---|
| | Carbosulfan (CS) | Carbofuran (CF) | Total Carbamates (CS + CF) | |
| <i>Experiment 1</i> | | | | |
| 1 | 0.782 | 0.042 | 0.824 | 0.3 |
| 2 | 0.288 | 0.041 | 0.329 | 0.3 |
| 3 | 0.194 | 0.029 | 0.223 | 0.3 ^c |
| <i>Experiment 2</i> | | | | |
| 1 | 0.243 | 0.013 | 0.256 | 0.3 ^c |
| 2 | 0.165 | 0.025 | 0.190 | 0.3 |
| 3 | 0.157 | 0.034 | 0.191 | 0.3 |

^aValues from dislodgeable residue tables.

^bSafe reentry level is 0.3 $\mu\text{g}/\text{cm}^2$ for CS, CF, and total carbamates (CS + CF) according to Iwata et al. (74).

^cReentry interval is 3 days for experiment 1 and 1 day for experiment 2.

Source: Nigg et al. (75).

TABLE 14. Calculation of Reentry Intervals According to U.S. Environmental Protection Agency (12) Guidelines^a

| Days After Spraying | Compound Ratio CS:CF |
|---------------------|-------------------------|
| 1 | 18.6: |
| 2 | 7.0: |
| 3 ^a | 6.7: |
| 1 | 18.7:1 |
| 2 ^a | 6.6:1 |
| 3 | 4.6:1 |

^aA slight modification of residues present on the foliage.

^bRatios calculated from data from dermal dose-ChE response curve.

^cNo effect level (NOEL) calculated from data from dermal dose-ChE response curve. $\text{NOEL} = \text{ED}_{10}(25 \text{ cm}^2)/(0.23 \text{ kg}\cdot\text{day})$. Predicted $\text{ED}_{10} = [P_1/\text{ED}_{10,1} + P_2/\text{ED}_{10,2} + \dots + P_N/\text{ED}_{10,N}]^{-1}$, where P_i = proportion of component in mixture (Finney, 72). ED_{10} values were extrapolated from Fig. 19. ED_{10} values for CS, CF, and HCF were 11.5, 6.24, and 98.8 $\mu\text{g}/\text{cm}^2$, respectively.

^dAllowable exposure level (AEL) = NOEL/SF . Safety factor (SF) = 10.

^eFrom total dose the reentry level was determined from the graph of whole-body dermal dose ($\mu\text{g}/\text{h}$) versus dislodgeable foliar residues (ng/cm^2) from the data of Pependorf and Lellingwell (44). Total dose was divided by 5.100 cm^2 .

^fReentry interval (total carbamates) according to experiment 2.

Source: Nigg et al. (75).

provide dislodgeable residues on the foliage at the same toxic organophosphorus level.

The transfer coefficient for California was used by repeat worker exposure data in this chapter yielded a k_d of 5.1 cm^2/h . Pependorf and Lellingwell (44) determined dislodgeable residue data from the leaf. Iwata et al. (73) determined residue data in terms of a two-sided reentry interval. Iwata et al. (74) divided the residue data by an unnecessarily long reentry interval. The Environmental Protection Agency (12) and Iwata (71).

TABLE 14. Calculation of Reentry Intervals According to U.S. Environmental Protection Agency (12) Guidelines^a

| Days After Spraying | Compound Ratio ^b CS:CF | NOEL ^c ($\mu\text{g}/\text{kg}\cdot\text{day}$) | AEL ^d ($\mu\text{g}/\text{kg}\cdot\text{day}$) | Total Allowable CS + CF Dose ^e ($\mu\text{g}/\text{h}$) | CS + CF Reentry Level ^f ($\mu\text{g}/\text{cm}^2$) |
|---------------------|--------------------------------------|---|--|---|---|
| <i>Experiment 1</i> | | | | | |
| 1 | 18.6:1 | 1198 | 120 | 1050 | 0.21 |
| 2 | 7.0:1 | 1131 | 113 | 989 | 0.19 |
| 3 ^g | 6.7:1 | 1127 | 113 | 989 | 0.19 |
| <i>Experiment 2</i> | | | | | |
| 1 | 18.7:1 | 1199 | 120 | 1050 | 0.21 |
| 2 ^g | 6.6:1 | 1125 | 113 | 989 | 0.19 |
| 3 | 4.6:1 | 1087 | 109 | 954 | 0.19 |

^aA slight modification of these guidelines is introduced here, which takes into account all toxic residues present on the foliage.

^bRatios calculated from dislodgeable residue tables.

^cNo effect level (NOEL) calculated from data from dermal dose-ChE response curve (Iwata et al., 74). $\text{NOEL} = \text{ED}_{10}(25 \text{ cm}^2)/(0.23 \text{ kg})$. Effective ED_{10} for mixture from $1/\text{ED}_{10} = P_1/\text{ED}_{10,1} + \dots + P_N/\text{ED}_{10,N}$, where P_i = proportion of component i in the mixture (Finney, 72). $\text{ED}_{10,i}$ values were extrapolated from Fig. 19 Iwata et al. (74), and found to be 11.5 and $6.24 \mu\text{g}/\text{cm}^2\cdot\text{day}$ for CS and CF, respectively.

^dAllowable exposure level (AEL) = NOEL/SF . Safety factor (SF) = 10. ^eTotal allowable dose = $(\text{AEL})(\text{body weight, } 70 \text{ kg})/(\text{duration, } 8 \text{ h/day})$.

^fFrom total dose the reentry level is determined from a graph of whole-body dermal dose ($\mu\text{g}/\text{h}$) versus dislodgeable foliar residues ($\mu\text{g}/\text{cm}^2$) from the data of Popendorf and Leffingwell (44). Total dose divided by $5100 \text{ cm}^2/\text{h}$ is k_d for citrus for a one-sided dislodgeable residue.

^gReentry interval (total carbamates from Table 13) is about 3 days for experiment 1 and 2 days for experiment 2.

Source: Nigg et al. (75).

provide dislodgeable residue data and estimate reentry intervals in these states for the same toxic organophosphate or methylcarbamate insecticide.

The transfer coefficient ($k_d = 5.1$) developed by Popendorf and Leffingwell in California was used by Iwata et al. (73, 74) and Nigg et al. (75) to estimate exposure. A repeat worker exposure study carried out by Nigg et al. (64) and discussed in Section 4.2 of this chapter yielded a k_d value of $5.3 \text{ cm}^2/\text{h}$, in close agreement with the California k_d of $5.1 \text{ cm}^2/\text{h}$. Popendorf and Leffingwell (44) developed their graphs using one-sided dislodgeable residue data. They assumed that all the residue was present on the top side of the leaf. Iwata et al. (73, 74) and Nigg et al. (75) reported their dislodgeable residue data in terms of a two-sided residue. Popendorf and Leffingwell (44) suggest that the two-sided residue data be divided by 2 to obtain one-sided data. If this procedure is carried out, unnecessarily long reentry intervals would be required by the modified U.S. Environmental Protection Agency procedure (12) when compared to the method used by Knaak and Iwata (71).

7 DISCUSSION

The large number of variables associated with the reentry problem prevented researchers from coming up with an easy and quick solution to the problem. However, by dividing the problem up into three distinct parts—(i) dissipation of the foliar residue, (ii) transfer of the residue to the skin and clothing of workers, and (iii) percutaneous absorption/dermal dose—ChE response—the reentry problem was resolved. A substantially large number of studies were conducted dealing with the dissipation of the foliar residues. These studies involved such factors as air temperature, humidity, ozone concentrations in air, rain, dust, season of the year, and a variety of other factors. The studies indicated that all these factors played a role in the conversion of foliar residues to toxic products, such as oxons, and in the dissipation of these residues. Several simple equations were written by California Department of Food and Agriculture scientists in the early 1970s in an attempt to describe the overall process. The equations did not adequately describe the process and the problem was finally solved as indicated in this chapter.

The overall dissipation process is still best described by a dissipation curve on a graph for the parent pesticide and each of the alteration products. Additional transfer studies are being conducted to relate foliar residues to residues on skin and clothing of workers. In a number of these new and unpublished studies conducted in Florida, the transfer coefficients are somewhat different from those described in this chapter. The reason for the discrepancy between the old and new data is unknown, but the results suggest that additional studies may be needed to understand fully the transfer process and the multitude of variables involved.

The recognition that a safe level on foliage exists for each pesticide, and that the safe level of one pesticide is related to that of another pesticide by their ability to inhibit cholinesterase when applied to skin, provided a practical procedure for establishing safe levels for new pesticides when a foliar safe level was known for an old pesticide. Dermal dose—ChE response studies in the rat provided a simple and inexpensive way of relating

TABLE 15. California Reentry Intervals

| Pesticide | Crop | | | | | All Other Crops |
|---------------------------------|--------|--------|------|--------|------------------------|-----------------|
| | Apples | Citrus | Corn | Grapes | Peaches and Nectarines | |
| Anilazine (Dyrene) | 2 | 2 | 2 | 2 | 2 | 2 |
| Azinphosmethyl (Guthion) | 14 | 30 | — | 21 | 14 | — |
| Carbophenothion (Trithion) | 2 | 14 | 2 | 14 | 14 | 2 |
| Chlorpyrifos (Lorsban, Dursban) | — | 2 | — | — | — | — |
| Demeton (Systox) | 2 | 5 | 2 | 7 | 7 | 2 |
| Diazinon | — | 5 | — | 5 | 5 | — |
| Dicrotophos (Bidrin) | 2 | 2 | 2 | 2 | 2 | 2 |
| Dimccron (Phosphamidon) | 2 | 14 | 2 | 2 | 2 | 2 |
| Dimethoate (Cygon) | — | 2 | — | 2 | — | — |
| Dioxathion (Delnav) | — | 30 | — | 30 | 30 | — |
| Disulfoton (Di-syston) | 2 | 2 | 2 | 2 | 2 | 2 |

TABLE 15 (Continued)

| Pesticide |
|------------------------------------|
| Endosulfan (Thiodan) |
| EPN |
| Endrin |
| Ethion |
| Malathion |
| Methamidophos (Mor) |
| Methiocarb (Mesuro) |
| Methidathion (Suprac) |
| Methomyl (Lannate, Nudrin) |
| Mevinphos (Phosdrin) |
| Monocrotophos (Azoc Naled (Dibrom) |
| Oxamyl (Vydate) |
| Onydemeton-methyl (Metasystox-R) |
| Parathion-ethyl |
| Parathion-methyl |
| Parathion-methyl (encapsulated) |
| Phorate (Thimet) |
| Phosalone (Zolone) |
| Phosmet (Imidan) |
| Propargite (Omite) |
| Sulfur |
| TEPP |
| All category 1 pesticides |

^aFor all applications rates of 8 lb or less per acre

^bFor all applications rates of more than 8 lb per acre

^cFor all applications

^dAny reentry interval Madera, and Tulare

May 15 shall have a 90-day interval, which is reduced

footnotes a, b, and c

^eFor applications of less than 1 lb per acre

^fThe reentry interval is 14 days

^gWhen 1 lb or less per acre is applied

^hWhen more than 1 lb per acre is applied

ⁱFor applications of less than 1 lb per acre in Stanislaus, Merced, and San Joaquin counties, if the harvest, there is a 3-day

TABLE 15 (Continued)

| Pesticide | Crop | | | | | All Other Crops |
|----------------------------------|--------|---|-----------------|-----------------|------------------------|-----------------|
| | Apples | Citrus | Corn | Grapes | Peaches and Nectarines | |
| Endosulfan (Thiodan) | 2 | 2 | 2 | 2 | 2 | 2 |
| EPN | 14 | 14 | <i>h</i> | 14 | 14 | <i>h</i> |
| Endrin | 2 | 2 | 2 | 2 | 2 | 2 |
| Ethion | 2 | 30 | 2 | 14 | 14 | 2 |
| Malathion | — | 1 | — | 1 | 1 | — |
| Methamidophos (Monitor) | 2 | 2 | 2 | 2 | 2 | 2 |
| Methiocarb (Mesurol) | — | — | — | — | 7 | — |
| Methidathion (Supracide) | 2 | 30 | 2 | 2 | 2 | 2 |
| Methomyl (Lannate, Nudrin) | 2 | 2 | 2 | 2 | 2 | — |
| Mevinphos (Phosdrin) | 2 | 4 | 2 | 4 | 4 | 2 |
| Monocrotophos (Azodrin) | 2 | 2 | 2 | 2 | 2 | 2 |
| Naled (Dibrom) | — | 1 | — | 1 | 1 | — |
| Oxamyl (Vydate) | 2 | 2 | — | — | 2 | — |
| Onydemeton-methyl (Metasystox-R) | 2 | 2 | 2 | 2 | 2 | 2 |
| Parathion-ethyl | 14 | 30 ^{a,d} 45 ^{b,d} 60 ^{c,d} | 14 ^e | 21 | 21 | 14 ^e |
| Parathion-methyl | 14 | 14 ^e | 14 ^e | 14 ^f | 21 | 14 ^e |
| Parathion-methyl (encapsulated) | 2 | 2 | 2 | 2 | 2 | 2 |
| Phorate (Thimet) | 2 | 2 | 2 | 2 | 2 | 2 |
| Phosalone (Zolone) | — | 7 | — | 7 | 7 | — |
| Phosmet (Imidan) | — | — | — | 5 | 5 | — |
| Propargite (Omite) | — | 14 | — | 14 | — | — |
| Sulfur | — | 1 | — | 1 ⁱ | 1 | — |
| TEPP | 2 | 4 | 2 | 2 | 4 | 2 |
| All category 1 pesticides | 1 | 1 | 1 | 1 | 1 | 1 |

^aFor all applications with spray mixtures containing 2 lb or less of parathion-ethyl per 100 gal, with rates of 8 lb or less per acre, and a total of no more than 10 lb/acre in the previous 12 months.

^bFor all applications with spray mixtures containing 2 lb or less of parathion-ethyl per 100 gal, with rates of more than 8 lb/acre, or more than 10 lb/acre in the previous 12 months.

^cFor all applications with spray mixtures containing more than 2 lb of parathion-ethyl per 100 gal.

^dAny reentry interval for parathion-ethyl still in effect on May 15 in the counties of Fresno, Kern, Madera, and Tulare is extended to 90 days from the application date. All applications made after May 15 shall have a 90-day reentry interval except for any reentry interval still in effect on September 15, which is reduced to 30, 45, or 60 days, respectively, from the date of application, in accord with footnotes a, b, and c.

^eFor applications of 0.5–1.0 lb/acre of parathion-ethyl, there is a 7-day reentry interval. For applications of less than 0.5 lb/acre, the reentry interval is 2 days.

^fThe reentry interval for nonencapsulated parathion-ethyl on grapes in Monterey County is 6 days.

^gWhen 1 lb or less per acre of parathion-methyl is applied there is a 2-day reentry interval.

^hWhen more than 1 lb/acre of EPN is applied there is a 14-day reentry interval.

ⁱFor applications of sulfur in Riverside County during March and April, and in San Joaquin, Stanislaus, Merced, Madera, Fresno, Kings, Tulare, and Kern Counties from May 15 through harvest, there is a 3-day reentry interval.

one pesticide to another in terms of potency or ability to inhibit cholinesterase. This procedure simplified the process, because a transfer coefficient and an acceptable exposure level (AEL) were not required.

The conversion of the parent pesticide to one or more highly toxic alteration products increased the complexity of the process by requiring ChE potency data for each product and potency data for the mixture present on foliage during the dissipation process. The toxicity of the mixture (ED₁₀ or ED₅₀) was easily obtained using a simple equation.

California used the information obtained in these studies to establish reentry intervals for a number of organophosphorus and carbamate pesticides. Monitoring studies were conducted after the reentry intervals were established to determine if they were adequate to protect the health of field workers. Dislodgeable foliar residues were found to be below the calculated safe levels and no worker illnesses were associated with these levels. California has developed the most comprehensive regulatory response to prevent exposure during reentry. The current California reentry intervals specified in State Regulations are provided in Table 15.

REFERENCES

- G. E. Quinby and A. B. Lemon, *JAMA, J. Am. Med. Assoc.* **166**, 740 (1985).
- T. H. Milby, F. Ottoboni, and H. W. Mitchell, *JAMA, J. Am. Med. Assoc.* **189**, 351 (1964).
- Title 3, Article 23 (Group 2) Section 2480, California Administrative Code. California Department of Food and Agriculture, Sacramento, 1974.
- K. T. Maddy, *Residue Rev.* **62**, 21 (1975).
- S. A. Peoples and K. T. Maddy, *West. J. Med.* **129**, 273 (1978).
- J. B. Knaak, S. A. Peoples, T. Jackson, A. S. Frederickson, R. Enos, K. T. Maddy, J. Bailey, M. E. Dusch, F. A. Gunther, and W. L. Winterlin, *Arch. Environ. Contam. Toxicol.* **7**, 465 (1978).
- F. A. Gunther, G. E. Carman, and Y. Iwata, *Worker Reentry Safety in Citrus Groves*, Contract No. 4288 with California Department of Food and Agriculture. Department of Entomology, University of California. Riverside, 1976.
- Y. Iwata, *Residue Rev.* **75**, 127 (1980).
- S. A. Peoples and K. T. Maddy, *West. J. Med.* **129**, 273 (1978).
- M. D. Whorten and D. L. Obrinsky, *J. Toxicol. Environ. Health* **11**, 347 (1983).
- J. E. Casida, Mode of action of carbamates. *Annu. Rev. Entomol.* **8**, 39 (1963).
- U.S. Environmental Protection Agency, *Pesticide Assessment Guidelines, Subdivision K, Exposure: Reentry Protection*. USEPA, Washington, DC, 1984.
- J. S. Tobin, *Citrus Pickers Working in Trees Treated with Ethion Formulations, July 24 to July 31, 1970, FMC Corporation Oct 8, 1970*, Public report to Hearing Record for Emergency Regulations adopted June 22, 1970. Submitted Oct 8, 1970 by the California Department of Agriculture.
- T. B. Waggoner, C. A. Anderson, and D. L. Nelson, *Determination of the Hazards to Workers Picking Citrus Treated with Guthion Wettable Powder Formulation, Chemagro Corporation*, Public report to Hearing Record for Emergency Regulations adopted June 22, 1970. Submitted Oct 8, 1970 by the California Department of Agriculture.
- T. B. Waggoner, C. A. Anderson, and D. L. Nelson, *Determination of the Hazards to Workers Picking Citrus Treated with Guthion Spray Concentrate Formulations, Chemagro Corporation*, Public report to Hearing Record for Emergency Regulations adopted June 22, 1970. Submitted Oct 8, 1970 by the California Department of Agriculture.
- G. W. Ware, D. P. Morgan, B. J. Estes, W. P. Cahill, and D. M. Whitacre, *Arch. Environ. Contam. Toxicol.* **1**, 48 (1973).
- G. W. Ware, D. P. Morgan, B. J. Estes, W. P. Cahill, and D. M. Whitacre, *Arch. Environ. Contam. Toxicol.* **1**, 117 (1974).
- G. W. Ware and D. P. Morgan, *Arch. Environ. Contam. Toxicol.* **1**, 117 (1974).
- R. C. Spear, W. J. Popenдорф, and G. L. Ellman, *Occup. Med.* **19**, 117 (1974).
- W. W. Kilgore, *Residue Rev.* **62**, 21 (1975).
- Agricultural Field Workers, California Department of Food and Agriculture, Davis.
- G. Zweig, J. D. Anderson, and W. J. Popenдорф, *Federal reentry intervals for organophosphorus pesticides*, 103-112 (1980).
- U. S. Department of Health, Education and Welfare, *Temporary standards for organophosphorus pesticides*, 10715 (1979).
- T. R. Milby, *Reentry Intervals for Organophosphorus Pesticides*, Working Group Report, California Department of Food and Agriculture, Sacramento, 1974.
- U.S. Environmental Protection Agency, *Health-safety standards for organophosphorus pesticides*, 10715 (1979).
- E. Kahn, *Residue Rev.* **62**, 21 (1975).
- J. B. Knaak, K. T. Maddy, and W. J. Popenдорф, *Pharmacol.* **46**, 3 (1979).
- W. J. Popenдорф, *Residue Rev.* **62**, 21 (1975).
- U.S. Department of Health, Education and Welfare, *Subjects*, 45 CFR 101.11 (1979).
- R. D. O'Brien, *Toxicology of Pesticides*, Academic Press, 1979.
- A. Hirschberg, *Residue Rev.* **62**, 21 (1975).
- Y. Lerman, A. Hirschberg, and A. Hirschberg, *Farm Chemical Health and Safety*, 40 Code of Federal Regulations, 1979.
- Title 3, Food and Drug Administration, Section 6770 of the Federal Food, Drug, and Cosmetic Act, 1979.
- H. O. Michel, J. L. Ellman, and G. L. Ellman, *Pharmacol.* **46**, 3 (1979).
- D. P. Nabb and F. A. Gunther, *Arch. Environ. Contam. Toxicol.* **7**, 465 (1978).
- G. L. Ellman, K. T. Maddy, and G. L. Ellman, *Pharmacol.* **46**, 3 (1979).
- C. G. Humiston and J. B. Knaak, *Residue Rev.* **62**, 21 (1975).
- J. B. Knaak, K. T. Maddy, and W. J. Popenдорф, *Appl. Pharmacol.* **1**, 117 (1974).
- T. B. Gaines, *Toxicology of Pesticides*, Academic Press, 1979.
- T. B. Gaines, *Toxicology of Pesticides*, Academic Press, 1979.
- J. B. Knaak, P. S. Estep, and W. J. Popenдорф, *Residue Rev.* **62**, 21 (1975).
- J. B. Knaak, *Residue Rev.* **62**, 21 (1975).
- W. J. Popenдорф, *Residue Rev.* **62**, 21 (1975).
- J. B. Knaak, C. R. Morgan, B. J. Estes, W. P. Cahill, and D. M. Whitacre, *Cholinesterase Inhibitors and Sulfoxide, unpubl.*

17. G. W. Ware, D. P. Morgan, B. J. Estlesen, and W. P. Cahill, *Arch. Environ. Contam. Toxicol.* **2**, 117 (1974).
18. G. W. Ware and D. P. Morgan, *Arch. Environ. Contam. Toxicol.* **3**, 289 (1975).
19. R. C. Spear, W. J. Popendorf, J. T. Leffingwell, T. H. Milby, J. E. Davies, and W. F. Spencer, *J. Occup. Med.* **19**, 406 (1977).
20. W. W. Kilgore, *Human Physiological Effects of Organophosphate Pesticides in a Normal Agricultural Field Labor Population*. Food Protection and Toxicology Center, University of California, Davis, June 1977.
21. G. Zweig, J. D. Adams, and J. Blondell, Minimizing occupational exposure to pesticides: Federal reentry standards for farm workers (present and proposed). *Residue Rev.* **75**, 103-112 (1980).
22. U. S. Department of Labor, Occupational Safety and Health Administration: Emergency temporary standard for exposure to organophosphorous pesticides. *Fed. Regist.* **38**(83), 10715 (1973).
23. T. R. Milby, Report of the Task Group on Occupational Exposure to Pesticides to the Federal Working Group on Pest Management, Washington, D.C., January 1974.
24. U.S. Environmental Protection Agency, Farm-workers dealing with pesticides. Proposed health-safety standards. *Fed. Regist.* **39**(48), 9457 (1974).
25. E. Kahn, *Residue Rev.* **79**, 27 (1979).
26. J. B. Knaak, K. T. Maddy, M. A. Gallo, D. T. Lillie, E. M. Craine, and W. F. Serat, *Toxicol. Appl. Pharmacol.* **46**, 363 (1978).
27. W. J. Popendorf, R. C. Spear, J. T. Leffingwell, J. Yager, and E. Kahn, *J. Occup. Med.* **21**, 189 (1979).
28. U.S. Department of Health, Education, and Welfare. *Guidelines for Protection of Human Subjects*, 45 CFR 46. USDHEW, Washington, DC, 1981.
29. R. D. O'Brien, *Toxic Phosphorus Esters: Chemistry, Metabolism, and Biological Effect*. Academic Press, New York, 1960.
30. A. Hirschberg, and Y. Lerman, *Fundam. Appl. Toxicol.* **4**, 529 (1984).
31. Y. Lerman, A. Hirschberg, and Z. Shteger, *Am. J. Ind. Med.* **6**, 17 (1984).
32. *Farm Chemical Handbook*. Meister Publishing Co., Willoughby, OH, 1984.
33. 40 Code of Federal Regulations 162.10, July 1, 1983.
34. Title 3, Food and Agriculture, Chapter 6, Pesticides and Control Operations. Group 3, Article 3, Section 6770 of the California Administrative Code. September 16, 1986.
35. H. O. Michel, *J. Lab. Clin. Med.* **34**, 1564 (1949).
36. D. P. Nabb and F. Whitfield, *Arch. Environ. Health* **15**, 147 (1967).
37. G. L. Ellman, K. D. Courtney, V. Andres, Jr., and R. M. Featherstone, *Biochem. Pharmacol.* **7**, 85 (1961).
38. C. G. Humiston and G. J. Wright, *Toxicol. Appl. Pharmacol.* **10**, 467 (1967).
39. J. B. Knaak, K. T. Maddy, T. Jackson, A. S. Fredrickson, S. A. Peoples, and R. Love, *Toxicol. Appl. Pharmacol.* **45**, 755 (1978).
40. T. B. Gaines, *Toxicol. Appl. Pharmacol.* **2**, 88 (1960).
41. T. B. Gaines, *Toxicol. Appl. Pharmacol.* **14**, 515 (1969).
42. J. B. Knaak, P. Schlocker, C. R. Ackerman, and J. N. Seiber, *Bull. Environ. Contam. Toxicol.* **24**, 796 (1980).
43. J. B. Knaak, *Residue Rev.* **75**, 81 (1980).
44. W. J. Popendorf and J. T. Leffingwell, *Residue Rev.* **82**, 125 (1982).
45. J. B. Knaak, C. R. Ackerman, K. Yee, and P. Lee, Reentry Research: Dermal Dose Red Cell Cholinesterase Response Curves for Methomyl, Thiocarb, Methiocarb and Methiocarb Sulfoxide, unpublished report. California Department of Food and Agriculture, 1982.

46. J. B. Knaak, K. Yee, C. R. Ackerman, G. Zweig, D. M. Fry, and B. W. Wilson, *Toxicol. Appl. Pharmacol.* **76**, 252 (1984).
47. J. B. Knaak and B. W. Wilson, Dermal dose—cholinesterase response and percutaneous absorption studies with several cholinesterase inhibitors. *ACS Symp. Ser.* **273** (1985).
48. H. I. Maibach, R. J. Feldmann, T. H. Milby, and W. F. Serat, *Arch. Environ. Health* **23**, 208 (1971).
49. L. J. Mazuret, *Phosalone, Methyl-Azinphos and Parathion, Acute Percutaneous Toxicity in the Rat*, unpublished report, 1971.
50. F. A. Gunther, W. E. Westlake, J. H. Barkley, W. Winterlin, L. Langbehn, *Bull. Environ. Contam. Toxicol.* **9**, 243 (1973).
51. G. L. Smith and D. E. Little, *Calif. Agric.*, June, p. 13 (1954).
52. F. A. Gunther, J. H. Barkeley, and W. E. Westlake, Worker environmental research. II. Sampling and processing techniques for determining dislodgeable pesticide residues on leaf surfaces. *Bull. Environ. Contam. Toxicol.* **12**, 641-644 (1974).
53. Y. Iwata, J. B. Knaak, R. C. Spear, and R. J. Foster, *Bull. Environ. Contam. Toxicol.* **18**, 649 (1977).
54. F. A. Gunther, Y. Iwata, G. E. Carman, and C. A. Smith, *Residue Rev.* **67**, 1 (1977).
55. J. Kvalvag, D. E. Ott, and F. A. Gunther, *J. Assoc. Off. Anal. Chem.* **60**, 911 (1977).
56. Y. Iwata, G. E. Carman, and F. A. Gunther, *J. Agric. Food Chem.* **27**, 119 (1979).
57. W. E. Westlake, F. A. Gunther, and G. E. Carman, *Arch. Environ. Contam. Toxicol.* **1**, 60 (1973).
58. W. F. Durham and H. R. Wolfe, *Bull. W.H.O.* **26**, 75 (1962).
59. J. E. Davis, *Residue Rev.* **75**, 33 (1980).
60. W. F. Popendorf, *Am. Ind. Hyg. Assoc. J.* **41**, 652 (1980).
61. W. J. Popendorf, An industrial hygiene investigation into the occupational hazards of parathion residues to citrus harvesters. Ph.D. Thesis, University of California, Berkeley (1976).
62. National Aeronautics and Space Administration, *NASA Life Sciences Data Book*, 1st ed. U.S. Government Printing Office, Washington, DC, 1962.
63. N. Diffrient, A. R. Tilley, and J. C. Bardagiy, *Human Scale 1/2/3*. MIT Press, Cambridge, MA, 1974.
64. H. N. Nigg, J. H. Stamper, and R. M. Queen, *Am Ind. Hyg. Assoc. J.* **45**, 182 (1982).
65. W. F. Serat, *Arch. Environ. Contam. Toxicol.* **1**, 170 (1973).
66. W. F. Serat and J. B. Bailey, *Bull. Environ. Contam. Toxicol.* **12**, 682 (1974).
67. W. F. Serat, D. C. Mengle, H. P. Anderson, and E. Kahn, *Bull. Environ. Contam. Toxicol.* **13**, 506 (1975).
68. R. C. Spear, *The Reentry Problem: Perspectives on the Regulatory Implications of Recent Research*, unpublished paper. University of California, Berkeley, 1977.
69. R. C. Spear, W. J. Popendorf, W. F. Spencer, and T. H. Milby, *J. Occup. Med.* **19**, 411 (1977).
70. D. M. Richards, J. F. Kraus, P. Kurtz, and N. O. Borhani, *J. Environ. Pathol. Toxicol.* **2**, 493 (1978).
71. J. B. Knaak and Y. Iwata, The safe level concept and the rapid field method: A new approach to solving the reentry problem. *ACS Symp. Ser.* **182**, 23 (1982).
72. D. J. Finney, *Probit Analysis*, 3rd ed. Cambridge Univ. Press, New York, 1972.
73. Y. Iwata, J. B. Knaak, G. E. Carman, M. E. Dusch, and F. A. Gunther, *J. Agric. Food Chem.* **30**, 215 (1982).
74. Y. Iwata, J. B. Knaak, M. E. Dusch, J. R. O'Neal, and J. L. Pappas, *J. Agric. Food Chem.* **31**, 1131 (1983).
75. H. N. Nigg, J. H. Stamper, and J. B. Knaak, *J. Agric. Food Chem.* **32**, 60 (1984).

F
ASSI
HAZ