Minimizing occupational exposure to pesticides: Epidemiological overview*

By

JOHN E. DAVIES**, VIRGIL H. FREED***, HENRY F. ENOS**, ANA BARQUET**, CARMEN MORGADE**, and JOSEPH X. DANAUSKAS**

Contents

I. Introduction

By way of introduction we will give a little background as to how this seminar-workshop entitled "Minimizing occupational exposure to pesticides" came about.

The Western Regional Coordinating Committee-38 (WRCC-38), one of the two sponsors of this program, was constituted in 1979. The purpose of this committee was to involve the medical as well as the agricultural community in the past and future pesticide residue-oriented research. At the first meeting, the Chairman explained that the committee had been incorporated with the intent of trying to inject an "agromedical" rather than a purely agricultural approach to pesticide residue research. The ultimate goal was to develop research which would minimize occupational exposure to pesticides. This present seminar-workshop was planned to review all aspects of pesticide occupational exposure and the related health effects. To quote from the Chairman's letter of invitation to partici-

* The work which this publication is based upon was performed pursuant to grant #OH00626 with the Department of Health, Education and Welfare, National Institute for Occupational Safety and Health.

** Department of Epidemiology and Public Health, University of Miami School of Medicine, Miami, FL 33136.

*** Department of Agricultural Chemistry, Oregon State University, Corvallis, OR 97331.

Residue Reviews, Volume 75.

pate in the workshop he stated, "the expected outcome of the seminar workshop will be the formation of a new committee with board representation from the Agricultural Experiment Stations, the U.S. Department of Agriculture and interested public health professionals to plan and conduct future research on occupational exposure in all its aspects and to interpret the resulting research data in terms of human safety in the pesticide work environment." This objective goes much beyond the reentry issue because (1) applicator and mixer-loader poisoning (pesticide concentrate) as well as "picker" poisoning (pesticide residue intoxication) are embraced, and (2) chronic as well as acute exposure is of concern, *i.e.*, the goal is to minimize all occupational pesticide exposure.

This meeting, therefore, is timely from a scientific point of view; it is also very timely from a political point of view because the Environmental Protection Agency will soon present their preliminary draft—Subpart K "Reentry Data Requirements" for review by the FIFRA Scientific Advisory Panel. In the interest of resolving and clarifying the future needs and roles of reentry in the overall guidelines, the Scientific Advisory Panel is interested in the topic because of the growing importance of human pesticide exposure assessment. We believe some of us are going to wish that we could be looking at exposure assessment and minimization guidelines rather than reentry. At present the U.S. Environmental Protection Agency and FIFRA require a battery of acute, subacute, and chronic toxicity testings of several species as a prerequisite to registration or continued registration of pesticides. In addition, the quantitation of human pesticide exposure has become an essential ingredient of the RPAR process. Quantitation of risk is part of the risk-benefit equation in the decision making process. Again, there have been examples where the reduction of exposure through protective clothing has become a label requirement as part of the RPAR decision. The RPAR proceedings for chlorobenzilate is a typical case example of this and the events not only set a legal precedent but also set a public health one, since the continued use of a weak carcinogen was ultimately based upon the requirement for the worker protection through the wearing of protective clothing. Table I reviews the regulatory action against pesticide products containing chlorobenzilate. In the first column there are listed the RPAR triggers which indicated the Environmental Protection Agency's position with regard to this miticide, the second column reviews the Scientific Advisory Panel's comments, and the third column gives the final decision taken by EPA. You will note that in addition to cancelling the use of chlorobenzilate in certain areas, the Environmental Protection Agency required residue monitoring; they also required three generations of rat studies. Following the evaluation of the animal effects data, studies were required on applicators. Since the promulgation of this final position, BRADY and his colleagues (1980) have identified a laboratory methodology to quantitate human exposure to this pesticide, thus, facilitating validation of this session in terms of (1) carcinogenic risk and (2) determining the ex-

Table I. *Reguatory action against pesticide products containing chlorobenzilate.*

RPAR trigger/agency position	SAP comment/recommendation	Final EPA position
Oncogenicity originally the sole RPAR trigger and primary basis of Agency's regulator action (F.R. 5/26/76).	Data showed chlorobenzilate to be a weak carcinogen but prudent to reduce human exposure to the extent feasible.	Presumption of oncogenicity was not rebutted.
Reproductive effects not identified at time of RPAR but added the following analysis of rebuttal information (F.R. 7/11/78).	SAP believed that potential adverse reproductive effects to be as important as the potential oncogenicity.	Reproductive effects trigger included as result of rebuttal submissions.
Cancel all noncitrus uses of chlorobenzilate.	SAP recommended continuation of noncitrus uses under same conditions as citrus uses since alternative pesticides appeared to pose greater risks.	Cancelled all noncitrus uses because of no offsetting benefits; alternative pesticides are less hazardous.
Cancellation of citrus uses in Arizona because of lack of data on the need or use of chlorobenzilate.	SAP recommended continued registration in Arizona on the basis of inadequate justification to exclude *any* state.	Continued registration in Arizona on the basis of IPM and insect resistance considerations.
Continue cattle feed uses of citrus pulp from treated citrus fruits.	SAP took no position on this proposal.	To avoid *de facto* cancellation EPA will require residue monitoring.
Continue registration of citrus uses with additional studies required on: exposure (applicators and pickers); residue monitoring of citrus pulp, milk, and meat; metabolism and environmental fate.	SAP specifically recommended two studies: (a) Examination of sperm counts in applicators and (b) a 3-generation rat reproductive study to determine the NOEL.	Required a 3-generation rat study with applicator sperm count study to be considered following evaluation of animal effects data.
Require protective clothing and respirators for applicators and restrict use to certified applicators only.	SAP took no position on this proposal.	Required specific protective clothing and respirators through new labels and labelling.

posure assessment of the pesticides for its future approved uses. Several panel members are present at this seminar-workshop, and they will benefit greatly by the national and international experience of the participants of this conference.

As will be seen from your agenda, the subject of minimizing pesticide exposure has included three ingredients necessary for the epidemiologic studies of occupational pesticide exposures. These are: (1) types of exposure and population at risk, (2) health related effects, and (3) exposure assessment measures.

We have been asked to present an epidemiologic overview of this subject and perhaps can do so more expeditiously and simply through the use of figures. Figures 1 and 2 represent all three human pesticide exposure categories. The special concerns of this meeting relate to the exposures and health effects of the worker which stem from the acute and chronic exposure categories. Systemic poisonings and topical effects on the skin and eyes are one group of diseases which we shall discuss. They occur with acute exposures. The population at risk includes the work categories concerned with the manufacture, application, formulation, mixing and loading, and picking and thinning. The subcategorization of acute poisoning which delineates applicator poisoning and picker poisoning has been made owing to differences in exposure mechanisms, severity of illness, number of persons involved, and geographical and other risk factors.

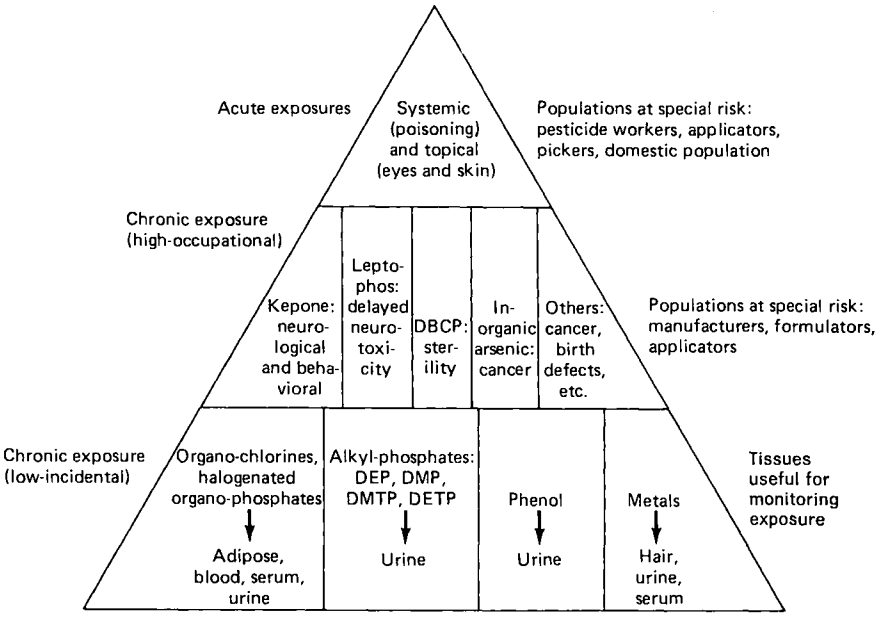

Fig. 1. Spectrum of pesticide exposure and some related health effects.

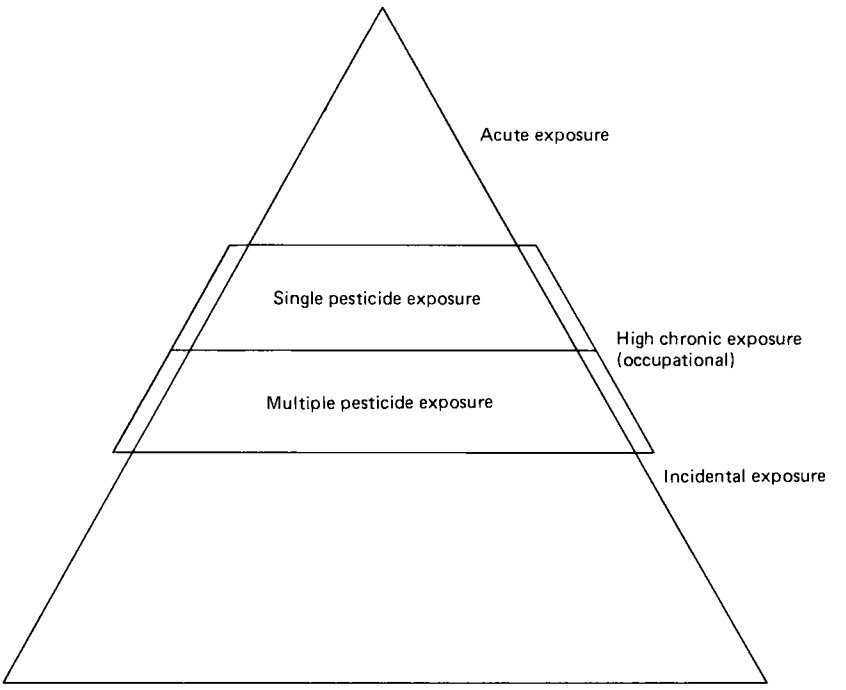

Fig. 2. Categories of human pesticide exposure.

At present in the United States, with current pesticide use patterns, the pesticide worker is at risk of both acute and chronic exposures, each of which can result in a variety of adverse health effects. Acute pesticide poisonings are still the main problem in developing countries where the technology of pesticide safety has not paralleled the transfer of agricultural technology. Today, in the United States, however, with the recognitions that such conditions as male sterility, neurological and renal disease, cancer and teratogenic effects, and behavioral disorders may be pesticide-related, the health significance of chronic exposure is becoming increasingly important.

These diseases have been identified in association with chronic pesticide exposure with exposure to a single pesticide only. Pesticides involved include dibromochloropropane, leptophos (an organophosphate insecticide), inorganic arsenic, and chlordecone (Kepone^{R}). The health-related effects were identified by epidemiological studies involving occupational exposure to single pesticides. In most instances, however, the pesticide exposure is multiple. Here is the area of great uncertainty and need for further study in the years ahead.

Improvements in the analytical methodology of the several exposure instruments used to conduct worker studies has greatly facilitated the determination of acute- and chronic-related effects.

II. Exposure instruments

Some of the more common examples of exposure instruments used in the past to assess worker exposure are: cholinesterase determinations, pesticide residue levels on alpha cellulose pads taped to the outside and the inside of the workers' coveralls, residue concentrations on gloves, residue levels in air samplers, and in and on foliar and soil samples. The use of the more important instruments are to be covered by future discussants. They are vitally important to the epidemiologist and we must know both their limitations and their strengths. We learned this in Florida recently in connection with the subsections below.

III. Mixed pesticide exposure studies

a) Comparison of exposure history and pesticide residues on external alpha cellulose patches

Red blood cell and plasma cholinesterase, exposure histories, and pesticide residues on external alpha cellulose patches were studied over a short period in three formulators occupationally exposed to a variety of pesticides. The history, the type of work, the pesticides formulated, and the pesticide identified, together with the cholinesterase findings in one worker are shown in Table II. In this worker and two other formulators, diazinon, Dursban[R], and methyl bromophos were identified daily on the patches. These three insecticides were identified every day irrespective of the work history. These data emphasized the multiplicity of small background exposures in mixed exposure situations.

In addition to these background data, the impact on formulation can clearly be seen. On days when one pesticide was being formulated, the pesticide could be detected on the patch in sizable quantities, particularly this was the case with methyl bromophos.

In addition, the impact of formulation can be recognized from the high concentrations methyl bromophos on day 2 and the residue levels of diazinon on day 3 in this small study, demonstrated the qualitative and semi-quantitative potential of the external patch. This was apparent even with the mixed exposure situations. The cholinesterase data were unremarkable and what one would have expected in view of the hazard of the chemicals being handled and the actual exposure sustained by the worker.

b) Comparison of exterior garment patches vs. interior garment patches

Since these studies were designed to measure pesticide penetration rather than develop total exposure assessment of the worker, interior and exterior garment patches were the major exposure instrument used. Only in this way could we determine true dermal exposure. These penetration studies were conducted at times when there appeared to be significant external exposures and are shown in Table III. They are

Table II. *Exposure history vs. exterior patches and cholinesterase data.*

Formulator	Day	Work description	Patches (25 cm², μg/ml)			
			Diazinon	Dursban®	Methyl bromophos	Malathion
#3—*J.L.T.*						
ChE (4 days prior):[a]						
RBC ChE 0.70						
Pl. ChE 0.60						
ChE—day 1:	1	Formulated Dursban 6#				
RBC ChE 0.52		9–11 a.m., Dithane				
Pl. ChE 0.62		M-45 2 p.m.–4 p.m.	4.0	20.6	19.4	2.6
	2	Formulated methyl bromophos				
		8 a.m.–1:30 p.m.,	2.6	2.2	29,300	N.D.[b]
		diazinon MG-8 from 2–4 p.m.				
	3	Formulated Dursban				
		10 a.m.–1:30 p.m.,	213	7.35	4.9	N.D.[b]
		diazinon 2–4 p.m.				
	4	Dowfume gases (filled tank)	2.43	1.42	6.45	0.08
	5	Dowfume gases (filled tank)	0.12	0.07	0.47	N.D.[b]
ChE—day 6:						
RBC ChE 0.50						
Pl. ChE 0.67	6	Unloaded freight car	0.06	0.13	0.67	N.D.[b]

[a] ΔpH/hr—Michel method.
[b] Not detected at limit of detectability.

striking, for they not only demonstrate the protective potential of the clothing but they also suggest the limitation of exposure assessment which is based on external patches alone. The concomitant alkylphosphate data shown in this table also highlight the complexity of alkylphosphate expressions when the exposures are mixed. In those circumstances when the metabolites identified are shared by one or more pesticides, it is frequently impossible to determine the actual exposure from each individual insecticide.

We have recently conducted pesticide protection studies in the field evaluating the penetration through 100% cotton-denim coveralls. The major findings contributed to our better understanding of work exposure because: (1) the protective potential of this approach was demonstrated, (2) the strengths and weaknesses of direct and indirect exposure instruments were recognized, and (3) the data suggested the methods of worker exposure in terms of clothing penetration and repellancy, and the contribution of an accidental spill from time to time to worker exposure.

IV. Single pesticide exposure study

Our experiences in protective clothing studies in citrus groves in Central Florida emphasize the simplicity and reliability of alpha cellulose patches and urinary excretion of alkylphosphate metabolite when a single exposure situation was identified.

We were invited to conduct case-control studies in two citrus grove companies in Orange County where ethion was being applied on a daily basis; ethion is an insecticide whose major urinary alkylphosphate metabolites are DETP and DEP. It was decided to determine efficacy on the basis of DEP excretion and % penetration identified on the basis of external and internal patches. This study was conducted with 8 mixers and 5 applicators. Their exposure was obviously significant and the format was as follows:

Phase 1—During this period the subjects were asked to wear their normal working clothes. Alpha cellulose patches were attached to the interior and exterior on opposing sides in the front of the shirt. Timed urine voids were collected in the field.

Phase 2—The same subjects were to repeat the first phase format but in addition were requested to wear OSHA/NIOSH-approved respirators for pesticide application during the mixing and application periods.

Phase 3—The subjects were issued 100% cotton-denim coveralls daily. These were of uniform design and weight and had been washed 6 times. These subjects were divided into two groups, one wearing treated and one wearing nontreated coveralls. During this study phase, respirators were not worn. In all three phases, patches and urines were collected daily. In the laboratory the alpha cellulose patches were received in labeled 60-ml, hexane-washed jars containing 10 cc of methylene chloride. The urinary alkylphosphates were analyzed by the SHAFIK and PEOPLES (1976) modified method.

Table III. *Pesticide penetration after intensive formulation exposures and after an accidental spill.*

Worker		Pesticide and metabolites	Patch (25 cm^2, $\mu g/ml$)		Penetration (%)	Type of clothing	Alkyl phosphates ($\mu g/ml$)	
			External	Internal			DMTP	DMP
Formulator	A.P.	Methyl bromophos (DMTP, DMP)	2,330	213	9	New & treated	0.30	5.8
	T.W.	Same	2,830	1,520	54	New & treated	0.25	6.72
	J.T.	Same	29,300	317	1	New & untreated	0.09	2.64
Pilot & mixer	B.R.	Dimethoate (Cygon^R), spill	6,650	0.04	0.001	New & untreated	—	—

V. Results of single pesticide exposure study

The individual personal clothing worn by the mixers and applicators in this study during the first and second weeks of study is shown in Table IV.

We measured the occupational exposure of these two groups (applicators and mixers) to ethion during the three phases of study. Their pesticide exposures with the different clothing modalities were determined on the basis of (1) the daily percentage penetration of ethion in each worker and (2) the daily creatinine-corrected urinary excretion of DEP in each worker. Results from wet patches, or patches which were dropped, were excluded in the compilation of the data.

For statistical evaluation of the different clothing modalities, we used "the unweighted means analysis of variance for repeated measures" because the two groups were unequal in size (8 mixers and 5 applicators) and each acted as their own control.

Table IV. *"Own" clothing characteristics of pesticide citrus grove applicators and mixers, Orange County, Florida, 1978.*

Subject no.	Type of clothing worn
1	Synthetic, short-sleeve shirts (thin), frequently open. Work pants cotton and/or synthetic.
2	Cotton shirts, sweat shirts, and "T" shirts occasionally. Work pants. Low shoes.
3	Primarily a thin, synthetic shirt and trousers. Occasionally synthetic/cotton shirts. Rubber boots.
4	Combinations: "T" shirts and short-sleeve shirts. Variety of work pants, light-weight.
5	Combinations of synthetic short-sleeve shirts (light-weight) and work pants. Low work shoes.
6	Fresh, very clean and pressed long-sleeve cotton shirt daily. Trousers cotton and/or synthetic. Ankle leather boots.
7	Variety of short-sleeve shirts, "T" shirts, and sweat shirts. Work pants varied from cotton twill to cotton synthetic.
8	Short-sleeve, cotton/synthetic shirt worn open. Thin khaki trousers. Low shoes.
9	A varied assortment of shirts, sweat shirts (long and short sleeve), and athletic jerseys. Trousers varied including shorts; sandals.
10, 11, 12, 13	Wore heavy army "fatigue" coveralls of a heavier twill finish than the University of Miami protective clothing. These military green fatigues were from a surplus store (no labeling to determine type and weight of fabric; long sleeve).

Table V. *Penetration of ethion in each of the pesticide workers wearing different clothing modalities in Orange County, Florida, 1978.*

		Penetration (%)		
		Phases 1 & 2	Phase 3	
Subject	Job	Own clothing & own clothing & mask	Untreated uniform	Treated uniform
R.S.	Mixer	47.3	8.1	5.9
D.O.	Mixer	20.8	3.9	0.3
R.S.	Mixer	16.1	0.4	0.6
P.M.	Mixer	21.0	0.3	0.8
J.N.	Mixer	40.6	9.0	4.7
G.G.	Mixer	42.6	0.3	0.8
J.C.	Mixer	20.0	2.4	0.0
W.B.	Mixer	12.4	7.7	16.0
	Mean of group =	27.6	4.0	3.6
	S.D.[a] ±	13.59	3.75	5.46
L.B.	Applicator	23.5	0.4	0.7
L.H.	Applicator	5.7	0.4	0.7
R.R.	Applicator	14.4	0.7	0.5
K.H.	Applicator	15.2	1.6	1.0
W.J.	Applicator	23.9	0.3	0.2
	Mean of group =	16.5	0.7	0.6
	S.D.[a] ±	7.52	0.54	0.29

[a] Standard deviation.

The average % penetration of ethion in each of the pesticide workers during phases 1 and 2 combined and phase 3 (treated and untreated) are shown in Table V. For the 8 mixers, the mean % penetration of ethion for the applicators was 16.5 during the first two phases as compared to 0.7 and 0.6 during phase 3.

The protective potential of these clothing modalities was also tested by urinary alkylphosphate excretions. The mean DEP concentrations during the several different clothing modalities worn by the groups are shown in Table VI. Average corrected DEP concentrations for the mixers was 1.05 when wearing their own clothing and 0.89 during phase 2 wherein they wore their own clothing and a respirator. The average DEP concentrations were 0.68 and 0.69 in phase 3 when these same workers wore new 100% cotton-denim coveralls.

The applicators were clearly less exposed than the mixers and the same downward trend was seen in each of the phases: 0.66 was the average corrected DEP excretion when applicators wore their own clothing but this declined to 0.64 when they wore a respirator and then fell to 0.31 and 0.36 when treated and untreated coveralls, respectively, were worn by this group.

Using the corrected urinary DEP concentrations as the exposure instrument, an analysis of variance showed there were differences among the modalities of protection which were significant at the $p < 0.01$ level.

Table VI. *Mean urinary DEP concentration (creatinine-corrected) observed with the different clothing modalities worn by citrus grove workers occupationally exposed to ethion, Orange County, Florida 1978.*

		DEP concentration (μg/mg)			
		Phase 1	Phase 2	Phase 3	
Subject	Job	Own clothing	Own clothing & mask	Untreated uniform	Treated uniform
R.S.	Mixer	1.82	0.91	0.87	0.93
D.O.	Mixer	1.92	0.98	0.76	0.44
R.S.	Mixer	0.65	0.59	0.49	0.55
P.M.	Mixer	1.16	0.80	0.52	0.79
J.N.	Mixer	0.70	0.77	0.93	0.78
G.G.	Mixer	0.91	1.20	0.91	1.13
J.C.	Mixer	0.89	1.64	0.80	0.61
W.B.	Mixer	0.32	0.21	0.17	0.25
	Mean of group =	1.05	0.89	0.68	0.69
	S.D.[a] ±	0.563	0.421	0.266	0.281
L.B.	Applicator	1.23	1.18	0.79	0.60
L.H.	Applicator	0.27	0.32	0.16	0.13
R.R.	Applicator	0.79	1.17	0.31	0.84
K.H.	Applicator	0.23	0.29	0.15	0.05
W.J.	Applicator	0.80	0.24	0.12	0.14
	Mean of group =	0.66	0.64	0.31	0.36
	S.D.[a] ±	0.418	0.489	0.280	0.342

[a] Standard deviation.

Urinary DEP concentrations for workers wearing their own clothing, with or without respirator, were significantly different from those observed when new uniforms were worn, whether treated or untreated; the mask did not significantly lower average DEP concentration values.

The effects of protective clothing were even more obvious when exposures were assessed on the basis of % penetration. The differences between % ethion penetration in workers wearing their own clothing when compared to the penetration observed when the new clothing (untreated or treated) was worn was shown to be significant at the $p < 0.001$ level. Once again there was no statistical difference between untreated and treated new uniforms.

When the applicators and mixers were studied separately, the applicators had lower average corrected DEP values, almost but not quite statistically significant ($0.05 < p < 0.10$). With regard to % penetration, however, the difference between the mixers and applicators was significant at the $p < 0.05$ level. The mixers' average % penetration was 27 against 16.5 for the applicators', *i.e.*, showing they had 11% higher penetration than applicators.

The beneficial effects of protective clothing are strikingly shown in Figures 3 and 4 when exposure in applicators was assessed on the basis

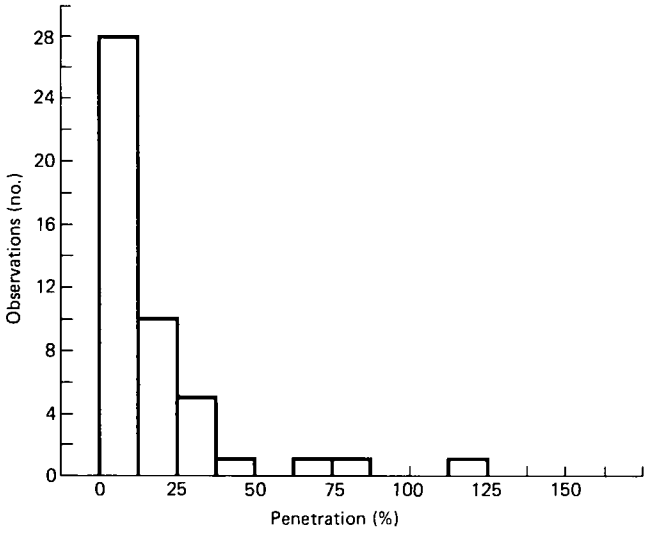

Fig. 3. Penetration of ethion in 5 pesticide citrus grove workers (Applicators) wearing their normal work clothes, Orange County, Florida, 1978.

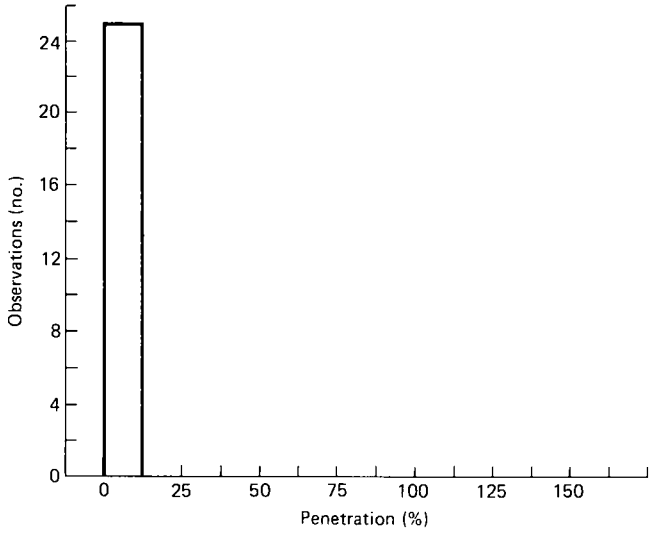

Fig. 4. Penetration of ethion in 5 pesticide citrus grove workers (Applicators) wearing new treated and new untreated uniforms, Orange County, Florida, 1978.

of % penetration when they wore their own clothing and when the 100% cotton-denim new uniforms were worn.

This is what epidemiology is all about: risk identification and risk reversal. The solutions may be multiple.

References

BRADY, S. S., K. A. LEVY, and H. F. ENOS: Chlorobenzilate residues in urine. Submitted Bull. Environ. Contam. Toxicol. (1980).

SHAFIK, T. M., and A. J. PEOPLES: Benzyl derivatives of urinary alkylphosphates. Presented Amer. Chem. Soc. Meeting, San Francisco, CA, Sept. 3 (1976).

WINER, B. J.: Statistical principles in experimental design. New York: McGraw-Hill (1962).

Manuscript received February 19, 1980; accepted April 1, 1980.