Table I. Effect of Fluorine-Free Water-Grown Diet on Weight and Dental Caries in Rats

	Number	Average Weight, Grams 22 days	88 days	No. of Carious Molars per Rat
Controls	18	41.2	128.1	0.5
Fluorine-free diet	19	40.8	51.2	10.2

Table II. Effect of Iodine-Free Water-Grown Diet on Thyroid Weight in Rats

	Number	Average Weight, Grams 22 days	88 days	Thyroid, Mg./100 G. Body Weight
Control	14	39.6	147.0	8
Iodine-free diets	17	41.3	99.2	26.4

tions made from the same varieties of plants but grown in soil. The basal diets comprised 30% yellow corn, 30% sunflower seed, 20% sunflower leaves, 10% yeast, and 10% sucrose. The test diets then were made by adding sodium salts or halogens, except the one which was to be absent for the test. At the end of the experiments after 2 months, tissues of liver, pancreas, spleen, kidney, stomach, uterus, thyroid, parathyroid, pituitary, adrenal, and thymus of representative rats were studied by histological methods, and the teeth and bones were studied by x-rays and chemical analysis.

The results of rat feeding in a sample experiment are shown in Tables I and II. The rats either failed to grow or grew at subnormal rates with diets deficient in either fluorine or iodine. Most of the molar teeth in rats on fluorine-free diets were carious (Figure 1). Normally grown crops comprised the diet of the control rats, whose drinking water contained 20 p. p. m. of fluorine. The thyroid gland of the control rats averaged 8 mg. per 100 grams of body weight, but on the iodine-free diet, the thyroid gland weighed 18 to 42 mg. per 100 grams of body weight. In other words, the rats had goiters.

In one experiment, six rats were placed on a sodium-free diet and these showed a subnormal growth rate, but six rats on a chloride-free diet showed no difference from the controls. Evidently there was enough chloride stored in the body at weaning to last for 2 months, the period of the experiment.

Discussion

Perhaps the most logical method of preparing diets devoid of any particular trace element would be to make a mixture of pure chemical substances lacking that element. Anyone who has prepared vitamin-free or calcium-free casein realizes the difficulty of extracting any particular component from a natural food substance. Furthermore, there is doubt as to whether all essential food components are known. The early name of vitamin B-12 was "animal protein factor" and was inadvertently added to diets. The use of amino acids instead of protein has not made the problem easier. The great difficulty of obtaining a diet devoid of iodine has led to the use of iodine antagonists (thiouracil, etc.). Such substances have other antioxidant effects as well as antagonizing iodine. The growth of a foodstuff devoid of any element depends on whether that element is essential to the plant. It has been claimed that iodine stimulates the growth of certain plants and it is thought that sodium may replace part of the potassium in certain other plants; but the authors have demonstrated that halogens or sodium are not essential for the crops they grew.

Acknowledgment

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Pesticide Toxicity Can Be and Is Being Avoided

PESTICIDES FORMULATION

Relation to Safety in Use

WAYLAND J. HAYES, Jr., and GEORGE W. PEARCE
Communicable Disease Center, Public Health Service,
U. S. Department of Health, Education, and Welfare, Savannah, Ga.

In arriving at improved safety of formulations, substitution of less toxic active ingredients, and use of emetics, warning colors, and antidusting agents and compounds to retard absorption are important. Highly toxic compounds may be employed with markedly decreased hazard if prior consideration is given to the incorporation of safety factors into the formulation itself, in addition to precautions usually advised.

Factors in pesticidal formulation which may lead to greater safety in their use are enumerated here, and certain examples are discussed. Very little has been written on this specific subject, although it is worthy of extensive consideration.

Increasing Safety of Formulations

The safety of formulations may be increased in a number of ways, but not all of them are applicable to any single situation. Some remarkable successes have been achieved in recent years in developing relatively harmless pesticides.

Table I. Concentration of Parathion in Air during Mixing of Spray Solutions by Addition of Parathion Formulations to Water

(Micrograms per liter)

Ordinary WWP[a]		Antidusting WWP[a]	Liquid
3.95	2.43	0.17	0.06
3.24	0.27	None	Trace (0.03)
1.36	5.53	0.03	Trace (0.01)
0.28	0.69	None	Trace (0.02)
	2.58	1.62	...
	1.02	0.12	None
	2.50	Trace (0.07)	None
		0.09	None
		0.53	Trace (0.16)
		None	
		Trace (0.12)	
		1.68	
Mean 2.21	2.15	0.37	0.04

[a] Water-wettable powder.

However, the fact that hazardous chemicals remain in use is proof that safer but equally effective materials are not available at an economical cost. A toxic insecticidal chemical remains a safety problem, no matter how formulated. This fact should not discourage efforts toward improved formulation, even though such efforts cannot replace a careful, adequate, and continuing educational program to ensure safe handling.

The use of inherently less toxic active ingredients is the most obvious improvement that can be made in the formulation of a pesticide, and frequently this is the only change mentioned in discussions involving safety. The most striking example in recent years is the substitution of DDT [2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane] for lead arsenate. Instances of chronic lead poisoning associated with orchard spraying were reported in a paper so recent that it mentioned that the older material was then being replaced by DDT (*3*). Acute poisoning by lead arsenate and other arsenicals also was encountered. By contrast, there are no confirmed cases of chronic DDT poisoning; confirmed, uncomplicated cases of acute DDT poisoning are all associated with the accidental eating of a relatively large quantity of DDT, amounting in some instances to 20 grams of the technical material (*4*). The record of DDT has been so good that it has been necessary to emphasize at every turn that the compound is not harmless and should be used with appropriate precaution. It was not so necessary to emphasize the all too apparent dangers of the arsenicals.

Another striking example of the use of an inherently less toxic active ingredient is the substitution of warfarin [3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin] for a number of highly toxic, quick-acting rodenticides, including 1080 (sodium fluoroacetate). It has been clearly demonstrated that warfarin is at least equal, if not superior, to any of the old rodenticides from the standpoint of control. By contrast, it has an excellent safety record. It is true that ANTU (α-naphthylthiourea) has a good safety record, but it is useful only in a limited number of situations. Red squill has a good safety record, with only a few human fatalities ascribed to it; however, many have found it essentially useless as a rodenticide. There is still need for a highly efficient, safe, quick-acting rodenticide.

It may be that malathon [*S*-(1,2-dicarbethoxyethyl) *O,O*-dimethyl dithiophosphate], NPD (tetra-*n*-propyl dithionopyrophosphate), and some of the other new organic phosphorus insecticides which are less toxic to mammals will prove sufficiently effective to be substituted for parathion (*O,O*-diethyl *O-p*-nitrophenyl thiophosphate) and TEPP (tetraethyl pyrophosphate). Other examples could be added.

Development of Safe Formulations

Solvents In developing formulations with a maximum safety factor for any particular active ingredient, the solvent is certainly of great importance, for one or more solvents frequently constitute the bulk of liquid preparations.

Because DDT shows some chemical relationship to the common chlorinated hydrocarbon solvents, pharmacologists very early explored the possibility that its mode of action in mammals might be similar. Experience has shown that the action of DDT on the liver and kidney, the organs chiefly affected by the chlorinated hydrocarbon solvents, is of secondary importance. Even so, the suggestion that chlorinated solvents be avoided in formulating DDT (*5*) is still a good one.

Table II. LD_{50} Values of Parathion Formulations Applied Dermally to Female White Rats

(Mg. per kg.)

Formulation	LD_{50}	19/20 Confidence Limits
Xylene solution of technical product	10.9	7.9–12.9
Aqueous suspension of plain water-wettable powder	15.0	10.1–22.4
Aqueous suspension of antidusting water-wettable powder	18.0	14.0–22.9

The avoidance of solvents with a high inherent toxicity is, of course, indicated. Benzene may cause a severe depression of the bone marrow activity with consequent anemia, and should be avoided as a solvent for pesticides wherever possible.

Another danger inherent in many solvents is their flammability. In this regard, the chlorinated hydrocarbon solvents are relatively safe and this property must be kept in mind in evaluating their over-all safety applicability. The conditions of use must also be considered. Formulations that would be entirely too flammable for use in aircraft can be used safely in certain other situations.

Dusts Dusts serve as a vehicle or diluent in dry formulations and should be selected for nontoxicity just as liquid solvents are selected. In particular, this means holding the percentage of free silica to a minimum and avoiding the use of talc, one of the few silicates known to cause silicosis. There is little danger of silicosis to the person who uses dusts occasionally, but the exposure of the commercial applicator or mixing plant worker may be significant.

Over and above the threat of silicosis, all dusts are somewhat irritating to the respiratory tract. For this reason, and because of the toxicity of the active ingredient, the development of antidusting formulations is a marked improvement. Their use in water-wettable powders allows the worker who mixes suspensions in the field to encounter significantly smaller concentrations in the air. Table I shows the air concentration of parathion at the level of the worker's face during the mixing process in an apple orchard. During 1951 and 1952, the concentration of parathion averaged slightly over 2 micrograms per liter with ordinary wettable powder. In 1952, an average of 0.37 microgram per liter was found with an antidusting pow-

Table III. Mortality of White Rats Receiving Single Dose of Different 6.25% Dieldrin Formulations Dermally

(100 mg. of dieldrin per kilogram of body weight)

Formulation	Mortality Fraction[a]	%
Liquid concentrate	9/9, 10/11	95
Paste-type concentrate	3/10	30
Mayonnaise-type concentrate	2/5, 0/5	20

[a] Ratio of number dead to total number treated.

Table IV. Mortality of White Rats Receiving Single Dose of Different 2.5% Parathion Formulations Dermally

(Each at rate of 40 mg. of parathion per kilogram of body weight. In each instance solvent was xylene)

Formulation	Mortality	
	Fraction[a]	%
Parathion solution	10/10, 10/10	100
Parathion-DDT-rosin–Triton X-155[b] solution	1/10, 2/10	15
Parathion-rosin solution	5/10, 25/50	50
Parathion-DDT solution	3/10, 43/50	77
Parathion–Triton X-155[b] soln.	9/10	90

[a] Ratio of number dead to number treated.
[b] Emulsifier made by Rohm & Haas Co., Philadelphia, Pa.

der, and the highest value found (1.68 micrograms per liter) was smaller than the mean for the unimproved formulation.

It will be noted in Table I that the average concentration of parathion in the air associated with the mixing of sprays from liquid concentrates was less than 0.04 microgram per liter.

This almost certainly indicates that liquid concentrates offer less hazard so far as respiratory exposure is concerned. Considerations of this kind have led to the adoption of liquid concentrates in England and in Germany (*7*). In this country, it has been thought that the advantage of liquid formulations in regard to respiratory exposure will be overbalanced by their supposed greater hazard in regard to skin exposure. Actually, the dermal toxicity of xylene solutions of parathion is only slightly greater than the toxicity of water-wettable powders, as shown in Table II. It is argued, however, that the hazard of powders is less because they are less likely than liquids to adhere to the skin. The conditions of use in England and in the United States are not sufficiently similar to permit a comparison. It must be recorded, however, that no fatal accidents with parathion have been reported from England. The possibility that liquid formulations may have more over-all safety than any kind of dust or powder formulation of the same concentration is worth considering. This is true not only of concentrates, but also of formulations ready for use, including those dispersed by aircraft.

Granular preparations of insecticides have been used for the control of malaria mosquito larvae or soil insects, where the cover is too dense to permit direct treatment of the water or soil. The granules reach places that sprays or ordinary dusts cannot penetrate, and also reduce somewhat the hazard of respiratory exposure.

Pastes Among the solutions and emulsions, some formulations have been prepared to reduce absorption either by reducing the possibility of contamination or in some more subtle fashion. For example, as shown in Table III, paste- and mayonnaise-type emulsion concentrates of dieldrin (1, 2, 3, 4, 10, 10-hexachloro-6, 7-epoxy-1, 4, 4a, 5, 6, 7, 8, 8a-octahydro-1, 4, 5, 8-dimethanonaphthalene) were less toxic than ordinary concentrates of the same strength. This was true even though in the experimental procedure the thick materials were rather laboriously rubbed into the skin at the prescribed dosage. Actually, the safety factor is much greater than the figures indicate because, if contamination does occur with the paste- or mayonnaise-type preparations, the material does not spread on the skin but tends to stand up in a mound. Unlike a liquid preparation, most of it can be quickly wiped from the skin without the use of soap and water.

In connection with the organic phosphorus insecticides, some progress has been made in developing formulations from which mammals absorb the active ingredient less readily. In an effort to get a longer residual action and in the hope of finding some synergistic action against resistant houseflies, parathion was formulated with DDT and rosin. The effectiveness of the combination as a residual, when tested in the laboratory against DDT-resistant houseflies, was found greatly superior to equivalent dosages of DDT or parathion alone. On the contrary, white rats received marked protection from the parathion in the combination. Results are shown in Table IV. The dosage of parathion was identical in each instance.

The use of special emulsifiers to increase the safety of Systox (diethoxythiophosphoric ester of 2-ethylmercaptoethanol) formulations has been reported (*2*).

Protective Measures

Protective skin coatings do not involve pesticide formulations directly, but it may be possible to develop skin treatments which would partially protect workers from dermal exposure to certain chemicals. Theoretically, this protection could operate through chemical inactivation of the toxin or through preventing its absorption. It is, of course, of the greatest importance that skin treatments be rigidly tested before any confidence is placed in them—for example, a commercial, "oil-resistant" cream gave no protection whatever against the subsequent dermal application of dieldrin emulsions.

The use of emetics and the coloring of formulations are well-known ways of making preparations safer, but the usefulness of these methods is limited. Emetics have been used with rodenticides with some success. Antimony potassium tartrate is commonly combined with zinc phosphide, thallium sulfate, and arsenic trioxide. Combination of the tartrate with ANTU is unnecessary because of its low toxicity to humans and combination with 1080 is useless, because the latter poison acts too rapidly. Red squill has an inherent emetic property, and it is thought that this is a property of the toxic glycoside itself and not of contaminants. Unfortunately, the acceptability to rats of red squill and of other emetic rodenticide formulations is poor.

Color has been used to make rodenticidal formulations completely distinct from desirable food or potable water. Compound 1080 is now used only with the addition of nigrosine black.

Discussion

The introduction of the new synthetic organic compounds has permitted a marked increase in the use of pesticides, not only in agriculture but also in public health. Partly because of the cost factor but chiefly because of increased effectiveness, pesticides are now being used in many situations in which they have never been used before. Even for many old established uses, the tonnage of economic poisons employed annually is now greater than ever before. The very magnitude of the quantities used would seem to require more attention to the safety factor.

This question of safety, involving toxicity to plants, to useful animals, and to man, has an important bearing on any future increase in the use of pesticides. The literature on the phytotoxicity of pesticides and on ways of reducing phytotoxic effects by various formulating methods is rather voluminous, especially in the case of arsenical insecticides and copper-bearing fungicides. This work related to plants illustrates that real progress toward safer formulations can be made. More important, it is entirely possible that a review of the methods used in improving the safety of formulations for plants would indicate that these same methods could be applied in improving the safety of formulations to man and domestic animals.

The very limited data submitted here suggest that highly toxic compounds may be employed with markedly less hazard if prior consideration is given to the incorporation of safety factors into the formulation itself in addition to the precautions usually advised in its use. It is even within the realm of possibility that some of the fatalities which have occurred with parathion might have been avoided with safer types of formulations. The mortality experience with parathion seems to have stimulated a search for less acutely toxic materials, especially among the organic phosphorus compounds. Although this substitution is a desirable approach, one should not overlook the possibility that highly toxic compounds may be practical, especially if they lend themselves to increased safety through improved formulation. In fact, in some cases the substitution of a highly poisonous compound with no cumulative effect for a material having less acute but more residual toxicity may be desirable. The hazard in the use of the former type of compound on food products involves only the spray workers, while the latter potentially involves the whole population.

Irrespective of the type of toxic ingredient employed, the desirability of using improved formulations or other safety devices which tend to reduce intake through the skin, the respiratory system, or the digestive tract should be emphasized to all those connected with the pesticides industry.

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INSECTICIDE TOXICOLOGY

Manifestations of Cottonfield Insecticides In the Mississippi Delta

RICHARD E. L. FOWLER, Communicable Disease Center, Public Health Service, Department of Health, Education, and Welfare, Cleveland, Miss.

A survey of school attendance records for white children in one Delta county, mortality figures for the entire state of Mississippi, and morbidity figures for a Delta plantation hospital was undertaken to determine the possible toxic hazard from the use of modern insecticides. In all studies reported no evidence could be found that pesticides were the direct or indirect cause of any chronic disease or a contributing cause in diseases generally recognized as having other etiologies. A definite problem exists in relation to widespread use of toxic compounds by inadequately trained and sometimes careless people.

With the introduction of modern economic poisons of the chlorinated hydrocarbon and organic phosphorus groups, agricultural practices have undergone considerable revision. The widespread use of these toxic compounds obviously suggests the possibility of acute or chronic intoxication of the resident and particularly of the worker population. It is proper that all physicians should be alert to the possible dangers of new pesticides and that a continuing study of the toxicology of these materials should be made by trained specialists. This point of view should not be confused with the opinion expressed in a few highly publicized reports, both in the popular press (*5*) and in medical literature (*1*, *2*, *4*), which have caused considerable alarm.

The Yazoo-Mississippi Delta is an almost exclusively agricultural area specializing in cotton production. Large quantities of various insecticides are used, primarily for control of cotton insects. During the past 3 years, the Mississippi State Board of Health has been requested repeatedly to determine whether the large-scale use of the newer insecticides presents a toxic hazard to the population of the Delta. This board, being unable to initiate such an investigation at the time, relayed the requests to the Technical Development Branch of the Communicable Disease Center. Because such an investigation had not only local but also general interest, a study was begun in June 1952. Operations were centered at the Cleveland, Miss., Field Station, which is located in the heart of the Delta.

The Yazoo-Mississippi Delta is a flood plain lying between the Yazoo and Mississippi Rivers in northwestern Mississippi. It includes all or almost all of eleven counties and parts of seven more, as shown in Figure 1.

The area is farmed intensively and, because of its physical characteristics, lends itself readily to mechanized cultivation. Many large plantations of several hundred to several thousand acres are located there.

The Delta has been described as "one of the most highly specialized cotton-producing areas in the world" (*6*). This is perhaps not quite as true now as formerly, for some other crops are be-

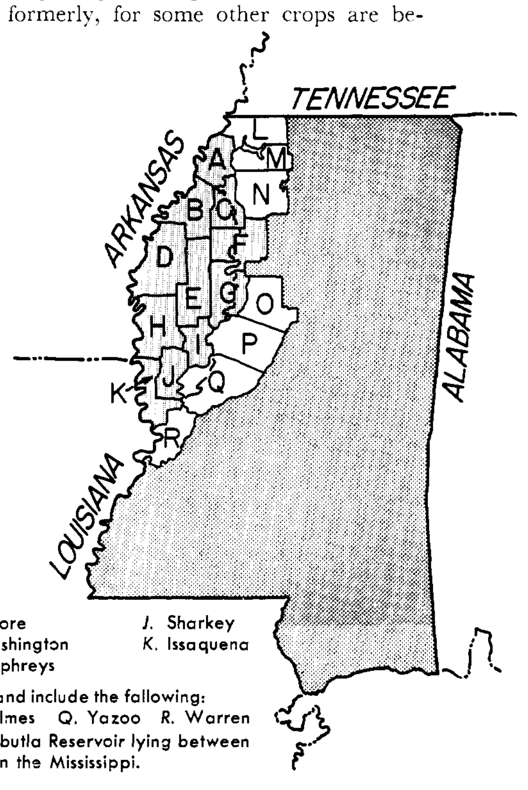

Figure 1. Map of the State of Mississippi showing the Yazoo-Mississippi Delta

Counties lying entirely or almost entirely in the Delta are stippled and are as follows:

A. Tunica B. Coahoma C. Quitman D. Bolivar E. Sunflower F. Tallahatchie G. Leflore H. Washington I. Humphreys J. Sharkey K. Issaquena

Counties lying partially in the Delta are not shaded and include the following: L. DeSoto M. Tate N. Panola O. Carroll P. Holmes Q. Yazoo R. Warren

Headwaters of the Yazoo River pass through Arkabutla Reservoir lying between DeSoto and Tate counties; the river flows south to join the Mississippi.