PN-AAE-329

REPRINT NUMBER

357

Furnished by
Communicable Disease Center
Technical Development Laboratories
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Reprinted from AGRICULTURAL AND FOOD CHEMISTRY, Vol. 10, May/June 1962, Page 240-244
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Stable Formulations for Sustained Release of DDVP

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DDVP has been formulated with a number of anhydrous, hydrophobic materials to produce a series of solid products containing up to 60% toxicant. These solid formulations, when properly prepared, are stable for long periods and readily release DDVP when exposed to the atmosphere or immersed in water. The most promising formulations contain montan wax and hydrogenated cottonseed oil or phthalic acid esters. Field trials have shown these formulations to be effective in controlling mosquitoes in primitive huts and also as a source of DDVP in bait stations for control of houseflies. The formulations described are expected to perform well in other confined or semiconfined spaces, such as greenhouses, storage bins, and warehouses.

The high vapor toxicity of DDVP 2,2-dichlorovinyl (dimethyl phosphate to insects led to its discovery by Mattson, Spillane, and Pearce (*8*). Since this discovery, the remarkable effectiveness of DDVP vapors against various species of insects, especially in the adult stage, has become well known. Observations on the extreme sensitivity of mosquitoes to DDVP vapors suggested that this technique might be used in the world malaria eradication programs (*5*). Laboratory experiments by Maddock and Sedlak (*4*) established that 0.015 μg. of DDVP per liter of air will give 100% kill of dieldrin-resistant mosquitoes (*Anopheles quadrimaculatus*) exposed for 4 hours.

In early experiments, Mathis and Maddock (*6*) used perlite impregnated with DDVP for the production of vapors in concentrations lethal to mosquitoes in simulated primitive huts. Although those experiments demonstrated the effectiveness of DDVP vapor, the formulation used as a source of vapor was unstable and therefore impractical for use in an operational program. The rate of decomposition of DDVP on perlite is shown in Figure 1. The formulation used for this study contained 10% DDVP by weight and the per cent decomposition was determined as follows:

A 2-gram sample was placed in a glass column and extracted with 100 ml. of 40% acetone-water. A 10-ml. aliquot of the extract was transferred to a separatory funnel and 50 ml. of water and 40 ml. of CCl_4 were added. After shaking, the CCl_4 layer was drawn off and the aqueous layer extracted again with 40 ml. of CCl_4. The CCl_4 extracts were combined and analyzed for phosphorus by a colorimetric method (*9*). This value was used to calculate the per cent of undecomposed DDVP in the formulation. The aqueous extract was analyzed for phosphorus similarly and the value used to calculate the per cent of DDVP decomposed on the carrier.

Other inert materials such as vermiculite, porous ceramic materials, ground corn meal, wool, and cotton were also impregnated with DDVP and the rate of decomposition was determined. The insecticide decomposed on all of these materials at about the same rate as observed for perlite, even when they were oven-dried prior to formulation. It is believed that the decomposition was due to traces of moisture which would be difficult to remove. In the presence of moisture DDVP is hydrolyzed, yielding primarily dimethylphosphoric acid and dichloroacetaldehyde.

Conventional mineral carriers as well as the other materials mentioned above, when mixed with DDVP, not only shorten the shelf life of the formulation, but also tend to absorb moisture from the atmosphere when put into use and, thus, subject the DDVP to further hydrolytic action. On this basis, conventional diluents and carriers appeared to be eliminated, and it was apparent that a carrier for DDVP was required which is anhydrous and also highly water-repellent or hydrophobic. Such a carrier might provide a formulation that not only would have good shelf life but also would be highly stable when exposed to atmospheric moisture or even when immersed in water.

With this in mind, attention was directed to cetyl and other higher alcohols; high molecular weight glyceryl esters, including animal and vegetable fats and oils and hydrogenated vegetable oils; and various waxes, including beeswax, carnauba, and montan wax. All of these materials mixed readily with DDVP when melted, and when the mixture was poured into a mold, most solifidied into a hard mass upon cooling. Using representatives of the above classes of materials, solid formulations containing up to 60% DDVP were successfully prepared.

Initial tests of the stability of DDVP in representatives of these types of materials were somewhat disappointing, although the rate of decomposition of DDVP was greatly reduced when compared to the perlite formulation. The presence of traces of moisture in the products was suspected, and experiments were conducted which established that this was the cause of the decomposition. Some typical data are presented in Figure 2. All formulations shown in Figure 2 contained 25% by weight of DDVP. Vacuum dehydration was carried out by heating the carriers to 90° C. under a vacuum of 0.05 mm. of Hg for 2 hours. After this treatment, the DDVP was added under an atmosphere of nitrogen. Samples of the untreated and vacuum-treated formulations were stored at ambient temperatures in an atmosphere of nitrogen in sealed containers. Samples were removed at intervals over several months and the per cent decomposition of the DDVP was determined by the following procedure:

From 0.2 to 0.5 gram of the formulation was dissolved in 20 ml. of carbon tetrachloride, after which 10 ml. of cold water were added. The mixture was stirred for about 30 seconds, and, as soon as the layers separated, the water layer was titrated with 0.01*N* NaOH, using phenolphthalein indicator.

Since the primary product of hydrolysis of DDVP is dimethylphosphoric acid, titration as a monobasic acid gives an accurate estimate of the hydrolyzed

DDVP. One milliliter of 0.01*N* NaOH is equivalent to 2.21 mg. of hydrolyzed DDVP. To obtain the total DDVP, whether decomposed or not, an excess of NaOH was added and the mixture refluxed for 10 minutes, after which the carbon tetrachloride was boiled off. The water solution remaining was diluted and a convenient aliquot analyzed for phosphorus (*9*).

Figure 2 indicates that stable formulations of DDVP can be made with montan waxes and hydrogenated cottonseed oil, if care is taken to use completely anhydrous materials. Although only a few of the other types of hydrophobic materials mentioned above have been tested, none should react directly with DDVP; and, as long as they are used in an anhydrous condition, stable DDVP formulations should result.

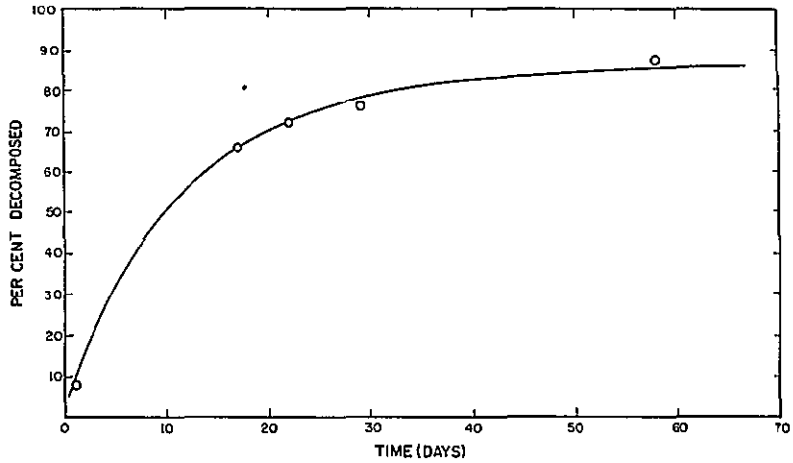

Figure 1. Rate of decomposition of DDVP on perlite

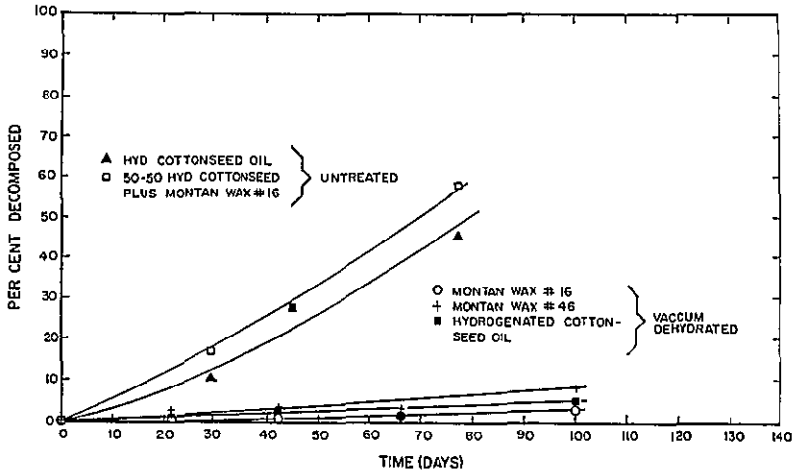

Figure 2. Effect of moisture on rate of decomposition of DDVP in hydrophobic carriers

Vaporization Rate

The insecticidal performance of the DDVP formulations based on waxes and the other hydrophobic materials mentioned above requires extensive and long-term testing. Thus, a laboratory procedure for measuring relative performance was needed. It seemed that under any given set of field conditions of temperature and ventilation, the effectiveness of a formulation would be primarily dependent on its vaporization rate per unit of surface. Its practical usefulness would also depend on how long it continued to produce vapor at a satisfactory rate. A laboratory procedure was developed which enabled the measurement of vaporization rates over any length of time desired and which gave reproducible results.

For rough estimates of the vaporization rate, the daily loss in weight of the formulation when placed in a Peet-Grady or similar chamber with nominal ventilation may be used. However, if no effort to control temperature and humidity is made, widely varying results are obtained from day to day and the data are satisfactory only when averaged over a relatively long period of time. The variation in weight loss is due primarily to variation in the amount of moisture on the surface of the formulation. To obtain more accurate and reproducible data on vaporization rate for any given formulation, the following empirical procedure was adopted:

Vaporizers were placed in glass containers immersed in constant temperature baths. Each container consisted of a 75-mm. O.D. glass tube about 45 cm. in length with 28/12 ball joints on the air inlet and exit ends. A Ŧ 71/60 joint near the top of the tube facilitated the introduction of the sample vaporizer, which was suspended by a wire from a small copper screen fastened in the upper portion of the tube. Inlet and outlet connections for the air were made through the 28/12 ball joints, the air being brought to temperature by passing it through copper tubing immersed in the same bath. An air-flow rate of 1 liter per minute was selected, so that only a small fraction of the saturation concentration was likely to be attained in the air stream. Since the volume of the container was approximately 1.3 liters, a complete change of air took place every 1.3 minutes. The outlet air was led through traps containing dilute NaOH, which trapped the DDVP. Fresh traps were installed at suitable intervals, and the phosphorus content of the trap liquid was determined from time to time. From these data, the amount of DDVP produced per unit of time could be calculated.

In any solid formulation of DDVP, a number of factors will operate to influence the rates of vaporization. The most important are: concentration of DDVP in the formulation, temperature, rate of diffusion of the DDVP in the formulation, and rate of air flow over the vaporizing surface.

Any rate measurements must be expressed in terms of a unit surface. Theoretically, humidity should not affect the vaporization rate, but experience with other types of vaporizers has shown that moisture can change the character of the vaporizing surface and thus affect the rate of loss of DDVP, especially if any appreciable amount of the phosphate moiety from decomposition of the DDVP collects at the surface. To eliminate the effect of humidity on the vaporizer surface, dry air was used in the empirical system for vaporization rate measurements described above.

Some data have been obtained on the influence on vaporization rate by the factors mentioned, and are presented below.

Effect of Concentration

The vaporization rate of DDVP from a given surface will be directly proportional to the number of molecules per unit of surface. Thus, if the concentration of DDVP in the formulation is doubled, the vaporization rate should be doubled. A limited amount of data obtained with DDVP formulated in a base containing 50% montan wax and 50% hydrogenated cottonseed oil indicates that this proportional relationship

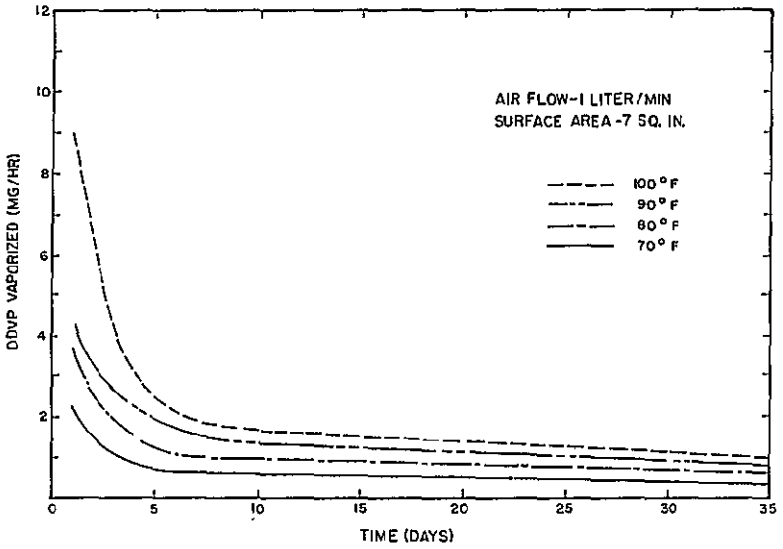

Figure 3. Effect of temperature on rate of release of DDVP vapor

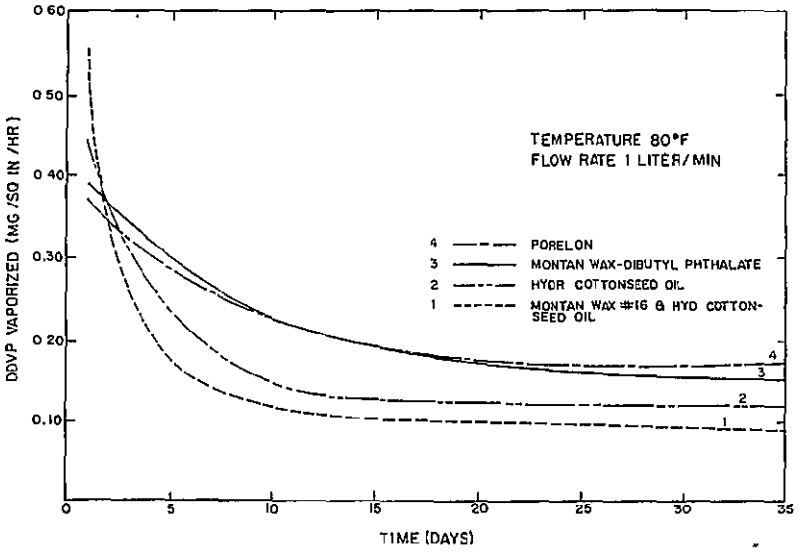

Figure 4. Effect of carrier on rate of release of DDVP vapor

1. 25% DDVP, 37.5% hydrogenated cottonseed oil and 37.5% montan wax No. 16
2. 25% DDVP and 75% hydrogenated cottonseed oil
3. 25% DDVP, 18.8% dibutyl phthalate, and 56.2% montan wax No. 16
4. 25% DDVP and 75% Porelon [polyvinyl chloride] product manufactured by S. C. Johnson & Son, Inc., Racine, Wis.]

holds true, at least approximately, when comparing concentrations of 25 and 50% DDVP. However, there may be rather wide divergence from this behavior in the case of other formulations, since a change in DDVP concentration may also alter the diffusion rate by changing the physical characteristics of the solid formulation. The effect of concentration will need to be evaluated for each formulation of interest. Normally the vaporization rate would be approximately proportional to concentration.

Effect of Temperature

Experience at this laboratory has indicated that the volatility of DDVP varies rather widely over ambient temperature ranges—e g., 60° to 100° F.

To evaluate the effect of temperature variation on the vaporization rate of DDVP from a wax formulation, four solid cylinders $^3/_4$ inch in diameter and $2^1/_4$ inches long were prepared from the following formulation: 37.5% montan wax No. 16 (American Lignite Products Co., Ione, Calif.), 37.5% hydrogenated cottonseed oil (Flake Gamma, manufactured by Wesson Oil and Snowdrift Co., Savannah, Ga.), and 25% DDVP (Norda Essential Oil & Chemical Co., New York 1, N. Y.). One cylinder was placed in each of four different vaporization chambers (described above) held at different temperatures—i.e., 70°, 80°, 90°, and 100° F.—and the vaporization rates were measured over a period of more than 30 days.

The curves shown in Figure 3 have been idealized somewhat because difficulties were experienced occasionally in maintaining a constant air-flow rate with the source available.

The initial rate of vaporization at any temperature is high, and the rate changes over the first week to a much lower level. This behavior is to be expected with a fresh surface because the number of molecules at the immediate surface is at its highest point. As the number of molecules at a fresh surface is reduced by vaporization, new molecules must diffuse to the surface; and as time goes on, the diffusion rate becomes more and more the limiting factor. After about a week, the change in vaporization rate with time becomes very gradual, and it would seem that the diffusion rate is the major controlling factor from then on. However, eventually DDVP-impoverishment of the vaporizer will begin to have an effect. The effect of temperature on the vaporization rate for this particular formulation is shown by the data in Figure 3. The rate approximately doubles for every 20° F. rise in temperature through the range studied.

Effect of Formulation Ingredients

From the start of this developmental work, it was believed desirable to obtain a solid formulation because liquid formulations would be too hazardous to use in practice on account of the high concentration of DDVP required to give a practical period of effectiveness. The montan wax would be the most practical hydrophobic carrier for reasons of economy, but when it was used alone with DDVP, there was excessive cracking and crumbling of the formation as it aged, which was deemed undesirable. The addition of cottonseed oil, hydrogenated cottonseed oil, phthalate esters, and other liquids usually eliminated this difficulty. Waxes, alone or combined with any of the other materials, produce vaporization rate curves similar in shape to those shown in Figure 3. However, the vaporization rate will vary, depending on the ingredients, because in most instances the diffusion rate will be different.

The influence of the formulation ingredients is well illustrated by the vaporization rate curves presented in Figure 4. These curves clearly indicate that the rate of vaporization can be varied rather widely, depending on the formulation ingredients. Of particular interest is that by substituting dibutyl phthalate for the hydrogenated cottonseed oil (curve 3 *vs.* curve 1), the rate of vaporization was almost doubled. Preliminary studies of the diffusion rate of DDVP in the two formulations represented by these curves indicate that the

diffusion rate for the dibutyl phthalate–montan wax formula (curve 3) is very much higher than that for the hydrogenated cottonseed oil–montan wax formula (curve 1). It seems clear from the data in Figure 4 and the limited amount of diffusion-rate studies available but not presented here, that diffusion rate will be a major limiting factor in controlling vaporization rate.

The Porelon formulation (curve 4, Figure 4) is a distinct departure from the other formulations studied. According to the manufacturer, this product has a microreticulated porous structure; and from curve 4 it is obvious that it releases DDVP at a rate equivalent to the best wax formulations.

Air Flow Rate over Vaporizing Surface

In practice, the air-flow rate would not seem to be of much importance except under extreme conditions of ventilation. It is, however, of vital importance in considering a laboratory procedure for measuring vaporization rates of candidate formulations. For example, in the system described previously and used to obtain the data given in Figures 3 and 4 the vaporization rate increased rapidly as the air-flow rates increased from 0.1 to about 0.8 liter per minute. Above this air-flow rate, the vaporization rate became constant. Thus, any procedure for general laboratory use will have to be carefully standardized and both the volume and flow rate of air specified.

Biological Performance

The formulations under consideration here have been tested biologically to some extent in two major applications: the residual fumigant technique in anopheline mosquito control and sugar-water bait stations in housefly control. For the purposes of this paper, only a brief report is given on their performance in these applications. Detailed reports will appear elsewhere.

Residual-Fumigant Studies. The formulation of montan wax–hydrogenated cottonseed oil–DDVP (Figures 3 and 4) has been tested extensively against adult *Anopheles quadrimaculatus* in Peet-Grady chambers and in simulated primitive huts. Vaporizing units were molded in the form of cylinders $1^1/_2$ inches in diameter and 5 inches long. These units performed sufficiently well in tests in Peet-Grady chambers so that tests in huts were deemed worthwhile. For hut tests, 1 to 9 units were used per hut (the huts were plywood with a total volume of about 1000 cu. feet) depending on degree of ventilation, and *A. quadrimaculatus* were exposed for 12 hours (8 P.M. to 8 A.M.). The formulation gave 100% kill under these conditions for periods up to 16 weeks (*7*). The concentrations of DDVP in the air were at practical levels, ranging from 0.005 to 0.35 μg. per liter. In an exploratory experiment in native mud housing in Wakara, Republic of Upper Volta, Africa, tests of cylinders of this formulation of the size described above indicated that a formulation which would produce vapor at a higher rate would be desirable. Studies of other possible formulations resulted in development of the montan wax–dibutyl phthalate–DDVP formula (Figure 4, curve 3). Tests of this formulation molded into units about $1^1/_2$ inches in diameter and 6 inches in length gave results far superior to those obtained with the montan wax–hydrogenated cottonseed oil–DDVP when tested in Peet-Grady chambers and in the simulated primitive huts using the same species of mosquito. This, of course, was in line with the results expected from examination of the comparative vaporization rate curves shown in Figure 4 (curves 1 and 3). After 12 weeks, the units of the improved formulation were still performing very effectively.

As a result of these tests, the dibutyl phthalate formulation was selected for testing in a field operation in Wakara, Republic of Upper Volta, Africa. The main objectives of this testing program will be to determine whether the residual-fumigant technique will reduce malaria transmission and to verify the safety to humans of DDVP vapors for this purpose at the air concentration levels needed for destruction of anopheline mosquitoes. In addition, the study will provide a field evaluation of the formulation.

Liquid Fly Bait Tests. The formulations developed in this work not only will act as sources of DDVP vapor for producing insecticidally active atmospheres but also will produce insecticidally active water solutions when immersed in such solutions.

Kilpatrick and Schoof (*2, 3*) have found DDVP to be extremely effective against adult houseflies when used in aqueous sugar solutions. Excellent control of flies in dairy barns was achieved by using specially constructed dispensers. One disadvantage to this method was that it was necessary for the user to measure liquid DDVP emulsifiable concentrate into the sugar solution each time the dispensers required recharging. If DDVP is incorporated in a solid wax formulation of the type described above, the toxicant will slowly bleed out into the aqueous sugar solution to maintain an effective bait for a long time.

In a limited field trial (*1*), a dairy near Savannah, Ga., was treated with 14 bait stations during the summer of 1960. One-quart chicken-watering devices were used to dispense the liquid bait. Each unit was charged with a quart of 10% sugar solution and one solid cylinder of montan wax–hydrogenated cottonseed oil–DDVP (curve 1, Figure 4) was added. Each cylinder weighed 20 grams and contained 5 grams of DDVP. Fly grill counts of 120 were observed on the day prior to treatment. The bait stations were operated for 10 weeks, during which the grill count never exceeded 16. The dispensing units were refilled with sugar solution three times during the test period, but the same cylinders were used throughout the test. Fly control for the period was rated as satisfactory to excellent.

Discussion

The use of wax-based formulations of pesticides is not new. However, application of waxes to a volatile and relatively unstable insecticide like DDVP is believed unique and increases the potential usefulness of DDVP very markedly. The major faults that apparently have limited the usefulness of DDVP have been its poor residual life and its sensitivity to moisture decomposition. Formulation in waxes corrects these faults to a great extent. In any case, wax formulations have excellent potential for preparing spontaneous vaporizing units for DDVP that have a practical life for use in malaria control programs; this was the major objective of the present work. In addition, wax formulations have been effective in fly control in water-bait stations. Wax formulations of DDVP are likely to prove useful also in controlling insects of both public health and agricultural importance that breed in or feed upon liquid media—e.g., mosquito larvae—or that occupy confined spaces that can be treated with such formulations—e.g., clothes moths. Whether the formulations would have much potential for field use in agriculture is not known, but it would appear that insecticidally active amounts of DDVP vapor could be introduced into any reasonably quiet atmosphere. Thus, for example, treatment of a densely growing field crop with a coarse granular form of a DDVP-wax formulation might be feasible, as well as treatment of greenhouses with formulations designed specifically for that purpose.

This is an initial report and, therefore, is very limited in scope. These types of formulations will undoubtedly be useful with other volatile insecticides in addition to DDVP. Much fundamental work remains to be done on the properties of these formulations and on methods of evaluating them both biologically and chemically. Moreover, the development of improved versions of the formulations described may be expected.

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Received for review July 18, 1961. Accepted October 13, 1961. Division of Agricultural and Food Chemistry, 139th Meeting, ACS, St. Louis, Mo., March 1961. Studies accomplished as part of a contractual agreement between the Communicable Disease Center and the International Cooperation Administration. Use of trade names is for identification purposes only and does not constitute endorsement by the Public Health Service.