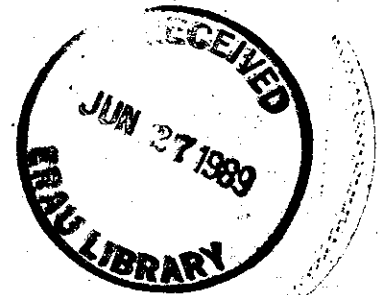


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**TOXIC HAZARDS
IN
AERIAL APPLICATION**

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ABSTRACT:

An analysis of the hazards accompanying the aerial application of toxic pest-control chemicals is presented. The nature of the chemicals, the symptoms of toxicity, recommended treatment, and suggestions for safe-handling, are discussed. ()

The introduction of the chlorinated, cyclic hydrocarbons for large-scale use as agricultural insecticides somewhat less than two decades ago, marked the beginning of a new era in agricultural pest control. In the intervening years, new chemicals, many of them engineered for specific agricultural purposes, have appeared in rapid succession. The large number and wide variety of these compounds, and their new and unfamiliar chemical and toxicological properties, have brought a host of medical problems.

The insecticides which were the farmer's first line of defense prior to the 1940's, presented no great toxicological threat. The compounds of arsenic, for instance, are dangerously toxic only when inhaled or taken by mouth, and these are routes of entry into the body which are relatively easy to protect. Mixtures of sulfur and lime are comparatively innocuous. Nicotine, derris, the pyrethrins and mercurials were never used for large-scale agricultural purposes as we now understand the term. There were no effective defoliants or weed-control chemicals.

Therefore, when the chlorinated compounds appeared in the 1940's and the organophosphates shortly thereafter in the 1950's, neither farmers nor pest control operators were prepared for the higher intrinsic toxicity of these substances. Nor were they prepared for the

appearance of symptoms without warning, due to a strange new hazard, absorption of the toxic agent through the skin.

It is not surprising therefore, that a familiar pattern has emerged. Many poisonings have occurred in the first months or years following the introduction of the more potent pesticides into a region where they were previously unknown. This is the pattern which enabled two Japanese scientists to accumulate the histories of 6000 cases of parathion poisoning within the first 5 years following the introduction of this chemical into Japan for use in the rice fields (1). Ultimately, instruction, training, and experience reduce the incidence of such poisonings.

There are so many insecticides, acaricides, herbicides, defoliants and other agricultural chemicals which present toxicological problems, that it would be impossible to describe the properties of each of them in a brief discussion. For instance, Volume III ("Insecticides") of the "Handbook of Toxicology" (2) contains almost 200 entries. Many of these are not adaptable to aerial application, and others present no serious toxicological problems. However, fifty or more of them are of sufficient commercial and toxicological importance to warrant

specific mention if time and space permitted, and many new agents are not listed.

If the magnitude of the problem seems large at this time, the future promises further complications. The organic chemist can alter and modify existing compounds of known effectiveness to produce an almost infinite variety of potentially valuable insecticides. While the number of individual agents can thus become quite large, it is fortunate, perhaps, that only a few types or classes of chemicals possess useful pesticidal activity. An effective insecticide must, at practicable dosage levels, disrupt or alter one or more of the basic life processes which are common to all animal organisms: transformation of energy by means of intracellular enzymes or catalysts; synthesis of essential cell constituents, including those necessary for growth and reproduction; transport of vital materials across cell membranes; communication by means of excitable tissues; or the biophysical phenomena involved in locomotion and circulation of body fluids.

The toxicological threat to man, from chemicals which are capable of altering these functions in lower animal forms, is obvious. It is also obvious that the hazards are exceptionally great to workers who manufacture and formulate these compounds, and to those who handle them in concentrated form in the field. Certain ones of these chemicals are so potent in their effects on man, that they are definitely dangerous, even after dilution for final application, whether by aircraft or other means. This fact is of particular importance to the applicator pilot, and to those concerned with his safety. As will be pointed out later, even mild exposure to certain insecticides can produce symptoms which would make it impossible for him to fly the precise patterns necessary in aerial application.

Some progress has been made in recent years, in producing chemicals which possess relatively greater toxicity for insects than for man. There is no reason for believing, however, that the time will ever come when those who handle agricultural pesticides can afford to ignore the basic safety practices which they must now follow.

It should be pointed out, in connection with the discussion which follows, that it is not possible to make a direct determination of the

dangerous dose of any drug or chemical for man. Such information must be obtained in a very "round-about" way. The relative toxicity of the individual members of a group of similar chemicals is first established by experiments on animals. This is usually done by determining the "LD₅₀" — the dose per unit of body weight which will kill 50 percent of a group of test animals. It is not possible to apply this figure directly to man, but it can be the basis for an estimate. If, for instance, the LD₅₀ of parathion for the rat is 4 milligrams per kilogram of body weight (about 2 mg./lb.), we can be fairly certain that 300 mg. would be dangerous for a 150 lb. man. Actually, we find that much less than this can be lethal. Occasionally an accidental poisoning occurs in a human subject, under circumstances in which the dose, the time, the manner of taking the compound, and other essential facts are known. Such an accident is the only means we have of establishing the true relationship between the actual toxicity for man and the estimate derived from animal experiments.

Probably 90 percent of all the compounds which possess useful pesticidal or herbicidal actions can be classified, on the basis of chemical composition and structure, into no more than a dozen major classes. Four of these contain the compounds which are responsible for almost all of the aerial applicator's toxicological problems; the nitrophenols, the carbamates, the chlorinated, cyclic hydrocarbons and the organophosphates.

The ovicidal, acaricidal and insecticidal properties of the nitrophenols have been recognized for many years. Concentrations which are effective for these purposes, however, are strongly phytotoxic, especially when applied in oil, and in recent years they have been used primarily as defoliants or herbicides. Typical of these compounds is 4, 6-Dinitro-2-methylphenol (dinitro orthocresol), which is perhaps more familiar under its trade names, Sinox, Antinonin or DNOC. These compounds must be classified as dangerous, since the toxic dose for experimental animals and man is contained in a relatively small volume of a commercial concentrate, and the effects are cumulative. DNOC is absorbed to an appreciable extent through the intact human skin. The toxic manifestations are similar to those produced by

dimetrophenol. They result from an action on individual cells in the organism, in which oxidative reactions are uncoupled from the phosphorylating mechanisms which yield useful energy for biological processes. The end result is a tremendous increase (as much as 4-fold), in the metabolic rate of the individual, to no useful purpose.

Early signs and symptoms of DNOC poisoning are excessive sweating, thirst, an exaggerated euphoria or feeling of well-being, followed by fatigue. If these signs and symptoms occur during the use of the chemicals in hot weather, they may be misinterpreted and ignored. This adds to their potential danger, for it is under these conditions that the body temperature may rise to dangerous heights and complete collapse follow. The course of acute poisoning from a massive, single exposure may be quite rapid. The onset is signalled by nausea and gastric pains. Restlessness, a feeling of intense heat, flushed skin, rapid breathing, fever and cyanosis follow, and death may occur within a few hours (3) (4). The dose necessary to produce such an acute death is estimated to be approximately 2 grams (4). This is probably in error on the "high side", and disturbing symptoms will result from a few hundred milligrams. There is no antidote, and the treatment is entirely symptomatic and supportive.

If any of the above signs of toxicity are detected, the subject should be removed from further contact with the agent for at least one week. Chronic toxicity may result from repeated, small doses. If a worker who has handled these compounds for several days or weeks complains of constant fatigue and an otherwise-unexplained loss of weight, he should be watched carefully and protected from further exposure for several days. If a concentrate of DNOC or other nitrophenol should come in contact with the skin, decontamination with soap and water should be immediate — not only to prevent absorption, but because these substances can cause painful skin irritation.

The use of the carbamates as pesticides is a fairly recent development. The group includes such familiar compounds as dimetan, Isolan, pyrolan and Sevin. Their basic chemical structure is ROC=ONHCH_2 . They are therefore closely related, both chemically and phar-

macologically, to the familiar therapeutic agents physostigmine and neostigmine. Like the organophosphates, they derive their insecticidal action from inhibition of the cholinesterase enzyme. Because of this action, they are potentially dangerous for man, as will be explained later. Acute toxicity studies on animals indicate that Isolan and pyrolan, for instance, are approximately one-half as toxic as parathion. Sevin appears to be somewhat less toxic than other members of this group. Their action on cholinesterase is not persistent, as is the case with the organophosphates, and their toxic effects are therefore not equally cumulative. In case of exposure, however, the onset of action is rapid, similar to the effects of such organophosphates as Phosdrin or TEPP.

The same safety precautions which apply to the organophosphates should be observed when these compounds are used. Should poisoning occur, the treatment consists of administration of atropine, artificial respiration if necessary, and of course, decontamination and removal from further exposure until recovery is complete. The duration of this isolation period must be left to the judgment of a physician, but should be no less than 24 hours if the symptoms have been mild, or several days if severe. Cholinesterase tests are of little practical value in carbamate toxicity. We still have much to learn about these compounds with respect to such factors as toxic dosage levels, the extent of absorption through the skin, and the rate of recovery from toxic effects.

The chlorinated, cyclic hydrocarbons comprise a large and heterogeneous group of compounds. They have now been in use longer, and their properties are generally better known, than is the case with any other class of insecticides. The names of several of them have in fact, become household words; DDT, lindane, chlordane. They vary widely in toxicity. The estimated fatal dose of DDT for an adult human male is 25 to 30 grams, taken orally. DDT is not appreciably absorbed through the skin. On the other hand, the estimated lethal dose of lindane, dieldrin or toxaphene is 2 to 7 grams. These compounds are readily absorbed through the skin, and the lethal dose by the percutaneous route is estimated to be from 3 to 5 times greater than the oral lethal dose. These figures may seem large, and the possi-

bility of exposure to dangerous amounts may appear remote. However, a simple calculation will show that a toxaphene concentrate containing 4 lbs. per gallon will contain 2 grams, a potentially lethal dose if taken orally, and harmful by any route, in less than one teaspoonful.

Since much smaller amounts than this can cause disturbing symptoms, the danger to those who handle such concentrated material is apparent. Applicator pilots are less likely to experience toxic exposure than ground-crew personnel, but many factors must be taken into account. For instance: the application desired may be heavy and the dilution factor low; the spray equipment may produce a fine aerosol under atmospheric conditions which cause it to settle slowly; the aircraft may pull large volumes of such contaminated air into the cockpit; the pilot may assist with the mixing and loading; he may fly for a longer period than is usual. Under any or all of these conditions he may be in danger of toxic exposure from both inhalation and surface contamination. It should be remembered that inhalation of a drug or chemical is roughly equivalent to intravenous injection with respect to the completeness of its absorption and the speed of onset of its effects.

The chlorinated compounds owe their insecticidal activity and their immediate or acute human toxicity to an action on the nervous system. Symptoms and signs take the form of nausea, dizziness, headache, tremor and weakness, proceeding in the case of large doses, to convulsions, dyspnea, cyanosis and circulatory collapse. The exact mechanism by which these effects are produced is unknown, and there is no specific treatment. Convulsions can be controlled by medium or long-acting barbiturates; other measures are symptomatic and supportive. There is a possibility of long-lasting or irreversible damage to liver or kidneys from chronic exposure, but there are no diagnostic tests which will reveal whether damage which a physician may detect upon examination has in fact resulted from contact with these agents. Certain members of the group possess actions which are not common to all. Lindane, for example, may cause cardiac arrhythmias, and chlordane may cause depression of the bone marrow, with a resultant reduction in the num-

ber of red and white blood cells. These effects are reversible if the individual is protected for a reasonable period, from further absorption of the chemical responsible.

The organophosphates also comprise a large group of chemicals. More than twenty compounds of this type are currently in use. Chemically, they are esters or thio-esters of an organic base with phosphoric or thiophosphoric acid. Like the chlorinated compounds, the individual members of this group vary widely in toxicity, and most of them are absorbed through the skin. They owe their insecticidal effectiveness and their human toxicity primarily to inhibition of the cholinesterase (more properly, acetylcholine-esterase) enzyme.

The significance and consequences of this action become clear from a consideration of the physiological importance of acetylcholine. Acetylcholine is the chemical agent which is responsible for the transfer of impulses at most of the points, in man or lower animals, where one nerve fiber connects with another or with an organ or tissue. This is comparable to the use of a relay in an electrical system to supply current to the final load. When a nerve impulse, which is electrical in nature, arrives at such a transfer point, acetylcholine is released from the terminal branches of the nerve almost instantaneously, and in high concentration. It excites the muscle, gland or connecting nerve fiber into activity, and then must be as quickly destroyed, just as a relay or contact must release quickly in an electrical system designed for repetitive action. Otherwise, the gland would continue to secrete, involuntary (smooth) muscle would continue to be affected, and voluntary (skeletal) muscle, after a preliminary stimulation, would become paralyzed. Also, acetylcholine would diffuse into neighboring areas, and selective, localized actions of single muscles or other tissues would be impossible. The rapid destruction of acetylcholine is provided for by the presence of cholinesterase at the nerve endings. The enzyme splits acetylcholine into two inactive fragments, choline and acetic acid. The organophosphates form a tight union with cholinesterase, and it cannot unite with, and destroy, acetylcholine. As a result, some degree of malfunction occurs in almost every organ and system in the body.

The properties of the specific organophosphate involved, the size of the dose and the manner of exposure affect the severity and order of appearance of the signs and symptoms of toxicity, but any or all of the following may occur: nausea, vomiting, visual disturbances, excessive sweating, excessive secretion of saliva and buccal and bronchial mucus; bronchiolar constriction, slowing of the heart, decreased blood pressure, anal and urinary incontinence, muscle twitching followed by brief convulsions, coma, pulmonary edema, muscular paralysis, respiratory failure and death. Certain of these symptoms may be deceptive. For instance, the pupil of the eye usually constricts, and the heart rate usually decreases. In early stages of poisoning, however, the pupil may dilate and the heart beat faster.

Unlike the carbamates and other cholinesterase inhibitors which have a short period of action, the effects of these agents are either persistent or irreversible. Recovery depends upon a combined process of slow reactivation and synthesis of new enzyme, and may require from one to three weeks. Their effects are, therefore, cumulative. An especially insidious feature of certain of these compounds, such as parathion, is that the onset of symptoms following a single cutaneous exposure may be delayed as long as 24 to 48 hours. Also, symptoms may appear on a day when exposure has been slight, because of residual effects from previous exposure.

Malathion, the O, O-Dimethyl thiophosphate of Diethyl mercaptosuccinate, is considered to be one of the least toxic of the organophosphates. It is considered to be even less toxic than DDT, and to this date there has been no authenticated report of a human fatality due to accidental occupational contamination with it. Chlorthion and Dipterex are other examples of organophosphates with low toxicity for man. In contrast to these, the estimated lethal, oral dose of compounds such as tetraethyl pyrophosphate (TEPP), Phosdrin, Systox (demeton) and parathion is from 20 to 100 milligrams (5). The fatal dose by percutaneous absorption is estimated to be from 2 to 3 times greater. A parathion concentrate containing 2 lbs. per gallon, contains about 250 milligrams per cubic centimeter. This amounts to two or three oral, lethal doses according to the most

conservative estimate, and is a potentially lethal dose by the percutaneous route, assuming complete absorption. Since 1 cc is about 20 drops, or 1/5 teaspoonful, it is apparent that compounds such as these are also dangerous after dilution.

A recent report indicates that a surprisingly large amount of a chemical may collect on body surfaces or be inhaled from a dilute solution during a spraying operation (6). The chemical involved was 2,4-dinitro-6-sec.-butyl phenol (DNOSBP), used in the appropriate dilution in an orchard application. Operators of ground equipment, under the conditions existing at the time of the test, collected the chemical on their body surfaces at the rate of 88.7 mg. per hour, and on respirator filter pads at the rate of 0.47 mg. per hour. Only one airplane was involved in the study, since it was primarily concerned with ground application, and only that material which collected on the hands of the pilot and flagman was measured. On this small area, the pilot collected DNOSBP at the rate of 0.2 mg. per hour. The corresponding rate for the flagman was 0.9 mg. per hour.

This aspect of aerial application deserves further study. Had the above study involved an agent as toxic as Phosdrin for instance, the implications are obvious.

The first, crucial step after known or suspected contamination of the skin, is a thorough cleansing with soap and water. Alcohol is a better decontaminating agent, particularly if the area of contamination is limited. In any event, speed is essential. It has been found that 30 minutes after a test application of parathion to the skin, vigorous scrubbing with soap and water will remove 80% or more of the material, and alcohol will remove most of the remainder. After 5 hours, however, 40% of a test dose will resist removal with soap and water, and 10% will persist after scrubbing with alcohol (7). Decontamination is especially important for the pilot who may be unconscious from accidental injury when found, if the possibility of chemical contamination exists.

First aid in organophosphate intoxication consists of the administration of atropine; by mouth if the symptoms are early and mild, subcutaneously or intravenously if the symptoms are prominent and syringes or hypodermic equipment available. Treatment in the field

should never go beyond a few such doses of atropine, in addition to such other emergency measures as may be indicated - artificial respiration, etc. The patient should then be rushed to a physician or a hospital for all further treatment.

Treatment has traditionally consisted of atropine in large amounts. In severe cases, 25 to 30 mg. or more may be given intravenously within the first 24 hours, usually in the form of 2 mg. individual doses. Atropine however, is not a complete antidote. It can control hypermotility of the gastrointestinal tract, dilate the bronchioles, correct most of the visual disturbances, and suppress the excessive secretion of saliva, mucus and sweat. It will not, however, correct all of the cardiovascular-pulmonary disturbances, and it cannot relieve the paralysis of the respiratory muscles and the central effects which together are responsible for respiratory failure. Artificial respiration with oxygen under slight positive pressure should be maintained until breathing resumes or other measures taken. At no time during treatment should a drug which depresses respiration (morphine, barbiturates, etc.) be used.

It was discovered comparatively recently that certain drugs known as aldoximes or notroso compounds (8), are able to disrupt the organophosphate-cholinesterase complex and reactivate the enzyme quickly. One of these, 2-pyridine aldoxime methiodide (2-PAM) has proved to be highly effective (1). It is available for use only under the direction of a physician. One gram of this drug is given in 24 hours, in individual doses of 0.2 gram, by slow, intravenous administration. The initial doses may be spaced closely and the intervals then lengthened, at the discretion of the physician. Treatment may be continued into the second day if necessary, but should not extend beyond 48 hours, and no patient should receive more than 2 grams. If the physician intends at the outset to use 2-PAM at some stage of the treatment, the amount of atropine should be reduced to avoid the late appearance of atropine toxicity if and when 2-PAM relieves the patient's symptoms.

Because of a fortunate physiological circumstance, the presence of cholinesterase in blood, it is possible to confirm the existence of organophosphate intoxication and to follow its course,

by a comparatively simple laboratory test. Two types of cholinesterase are, in fact, present in blood. One of these, in the plasma (or serum), is not specific for acetylcholine, and is termed pseudo-cholinesterase. The enzyme which is present within the red cells is apparently identical with that in nerve tissue. The activity of these enzymes is usually determined by one of three methods. One of these involves a colorimetric procedure. The other two take advantage of the fact that one of the products of acetylcholine hydrolysis is an acid, which can be made to release CO₂ from sodium bicarbonate, or change the pH of the reaction mixture. Either of these can be accurately measured.

The value of blood cholinesterase tests depends upon how and when they are made. Whole-blood or red-cell levels are more valuable than those of plasma or serum. It is advisable for each person connected with an aerial application team to have a test made at the beginning of the season, prior to any contact with organophosphates, to establish his normal level, since there is considerable variation between individuals. There is no direct correlation between the cholinesterase level and the severity of symptoms, but no person can have a normal value if he has absorbed appreciable amounts of an organophosphate by any route. Therefore, if tests are made with some regularity during the spraying season, they will reveal whether personnel are taking adequate precautions. They will also indicate whether the individual is in danger of experiencing symptoms from further, slight exposure. If a test is made at the time of an accident, it could support symptomatic findings in establishing whether or not chemical toxicity might have been contributory. Since the test itself is relatively simple, local laboratories should be persuaded to equip themselves for it, because of the difficulties involved in sending blood samples by mail to a central location.

The fact that our most effective pest-control chemicals are relatively insoluble in water, contributes to the hazards involved in preparing and applying them. The non-aqueous solvents used in liquid formulations (benzene, xylene, naphtha, kerosene, etc.) are flammable, and constitute a definite fire hazard. Certain ones of them are sufficiently volatile that pressure

may build up in a can of liquid concentrate which has been exposed to the sun. When such a container is punctured or uncapped, the pressure is relieved by an outward rush of solvent vapor, which may carry an appreciable amount of the more toxic insecticide with it. All liquid-concentrate and wettable-powder formulations contain emulsifiers or wetting agents. It is certain that these agents influence the rapidity and ease with which the liquid penetrates protective clothing and spreads upon the skin. It can be predicted that they also accelerate the rate of absorption through the skin, but this factor has not been adequately tested.

No specific mention has been made in this discussion, of the hazards involved in handling dusts. It should go without saying, that they can be as dangerous as liquid preparations. However, several factors make it somewhat simpler to protect against them: they require less preliminary handling than liquids; they are more easily blocked from contact with the body by coveralls and respirators; and they provide more obvious evidence of their presence on operator and equipment than do liquid materials.

Admittedly, this is a rather discouraging picture of the hazards involved in handling pest-control chemicals. It is not intended to frighten pilots and other personnel, but to alert them to the fact that constant vigilance is the price of safety; that to be forewarned is to be forearmed. It has been proved that safety is possible, by the generally good record of many who have handled the organophosphates and chlorinated compounds in large quantities for the past several years. Better equipment, such as bottom-loading systems for spray planes, newly-designed helmets with integral visors and masks for pilots, can be of help. For ground personnel, the fundamental principle of safety is more basic and simple; it consists of thinking in advance about each move, and making it deliberately. All members of an aerial-application team should observe each other for signs of toxicity; these are sometimes more obvious to others than to the victim himself. It should always be remembered that repeated, small exposures may constitute a greater danger than the large, single dose.

Two specific recommendations should be made to workers handling organophosphates:

- 1) Smoking is not advisable during or immediately after work periods. Nicotine in small doses can produce symptoms very similar in nature to those of the organophosphates. Even in the person who is habituated and somewhat tolerant to nicotine, there is a chance that the effects of the two agents might be additive.
- 2) The practice of attempting to suppress mild symptoms of organophosphate poisoning with atropine to avoid loss of time is extremely dangerous and should be discontinued. It has been pointed out that atropine does nothing to the voluntary muscle impairment, and it is possible to over-correct other symptoms such as constriction of the pupil.

With respect to protective measures and equipment, the following generalizations appear to be justified:

Each person connected with aerial application operations, whether "swamper" (mixer-loader), flagman or pilot, should have goggles, respirator and at least one spare coverall, available at all times, and should have access to a shower or an adequate supply of soap and water. A quart or more of isopropyl or denatured ethyl alcohol should be kept available for scrubbing areas of known, heavy contamination. Ground personnel should have, in addition, rubber or plastic boots and gloves. Wearing protective gear should be optional with ground crew and pilots if they are handling compounds no more toxic than DDT and Malathion, or mixtures of them. Ground crews should be required to wear full protective equipment, and to take all other reasonable precautions, when they work with compounds as toxic as toxaphene and parathion. Pilots should wear goggles and respirators under these circumstances, on their own volition. In certain areas of the United States, respirators are frequently considered unnecessary because there is sufficient wind to protect personnel from fumes and fine spray. For handling materials such as Phosdrin spray and TEPP dust, no precaution or protective measure should be overlooked.

Both farmers and applicators must accept some degree of responsibility for protection of the public from the hazards of chemical toxicity associated with pest-control operations.

The problem of drift has long been recognized, and all reasonable precautions are now being taken to avoid it. Precautions should also be taken to prevent persons from entering fields which have been freshly sprayed with the more toxic compounds, either by posting warning signs or by other means.

Discarded insecticide containers may constitute more of a menace than has previously been realized, and should be guarded carefully prior to disposal. It has been found, for instance, that an "empty" 5-gallon parathion drum which had contained 45.6 percent emulsifiable concentrate may contain as much as 10 gm of active parathion after months of exposure to the weather (9). This amounts of course, to many lethal doses for an adult human or a farm animal of equal size. Procedures designed to decontaminate such containers to a safe condition for handling and storage were tested. The most practicable method consisted of several rinses (2 or more) with plain water, but this did not make the drums safe for any secondary use. It is suggested, therefore, that containers should be rinsed if possible, and that in addition, they should be punctured or crushed to render them useless before impoundment for final disposition.

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