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Effects of Pesticides and Drugs on Working Memory in Rats: Continuous Delayed Response

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HEISE, G. A. AND J. D. HUDSON. *Effects of pesticides and drugs on working memory in rats: Continuous delayed response*. PHARMACOL BIOCHEM BEHAV **23**(4) 591–598, 1985.—Effects of four pesticides (carbaryl, propoxur, chlordimeform, and deltamethrin) and four reference drugs (physostigmine, scopolamine, methscopolamine, and chlordiazepoxide) were measured in two delayed response, working memory procedures: go-no go alternation in which rats initiated their own trials, and spatial reversals. Four of these compounds (carbaryl, propoxur, physostigmine, and scopolamine) were also tested in a go-no go alternation procedure in which animals did not initiate their trials. The pesticides and physostigmine did not selectively affect working memory in any of the procedures: low doses only moderately decreased response accuracy, whereas higher doses suppressed responding indiscriminately. The pesticides and physostigmine had similar effects on go-no go alternation (i.e., working memory) and analogous go-no go discrimination performance. Effects on go-no go alternation performance did not depend on whether the animals initiated their own trials. Scopolamine, in contrast, appeared to disrupt working memory. It profoundly disrupted accuracy at doses that only moderately decreased over-all responding and impaired go-no go alternation accuracy much more than discrimination accuracy.

Go-no go alternation Spatial reversals Discrimination Working memory Pesticides Carbaryl Propoxur Chlordimeform Deltamethrin Scopolamine Chlordiazepoxide

ALTHOUGH exposure to toxicants has been alleged to impair memory [12], few experiments have specifically examined the effects of toxic substances on working memory in animals (see [6] for review). This report describes the effects of four pesticides and four comparison drugs on performance of rats in two types of delayed response procedures for measuring working memory: go-no go alternation and spatial reversals.

The go-no go alternation and spatial reversals procedures are continuous discrete trial, working memory, delayed response procedures. They are *continuous* in that each trial is both the occasion for responding with respect to the alternative stimulus events from the preceding trial and also the occasion for the presentation of the stimulus ("sample") to be remembered on the next trial. They are *working* (rather than reference) memory procedures since the correct (reinforced) response on a trial is not invariant: it depends upon which particular stimulus events took place on the preceding trial [8, 9, 16]. They are *delayed response* (rather than delayed comparison) procedures since the correct response on a trial is determined entirely by the stimuli from the preceding trial, rather than jointly by the present and preceding trial stimuli.

Go-no go alternation baselines have been previously described [7, 15, 17]. In these procedures, the discrete trials are all signalled alike by illumination of the same panel light. "Go" trials, on which a press on the right lever produces reinforcement, alternate with "no go" trials, on which right lever presses do not produce reinforcement. The rats learn alternately to press and not to press the lever on successive trials. Thus responding on a trial is controlled by differential prior trial events (e.g., reinforcement or non-reinforcement, response or non-response) which the animal has somehow to "remember" over the intertrial interval.

Unlike the studies just cited, an omission procedure was used in the present go-no go alternation experiments: reinforcement (a drop of water) was delivered when the rat did *not* respond on no go trials as well as when it *did* respond on go trials. Experiment 1 examined the effects of two pesticides and two reference drugs on go-no go alternation performance when the trials were presented automatically at the end of the 5-sec intertrial intervals. The procedure in Experiment 2 was like that in Experiment 1, except that the animals were required to press the left lever (a "trial initiation response") in order to produce their right-lever alternation trials. This initiation requirement provided a sensitive measure of over-all responding and an objective basis for interpreting failures to respond on trials in the calculation of accuracy data. When the animal itself produces the trial, non-response on the trial is presumably controlled by the stimuli that the animal is discriminating or remembering. Conversely, trial initiation failures under these circumstances presumably reflect non-specific performance effects such as motor or sensory deficits, "inattention" or malaise. The behavioral specificity of treatment effects of the compounds was also tested in Experiment 2 in a go-no go "discrimination control" procedure. Accurate performance in the discrimination control procedure did not

involve working memory, since responding was controlled by discriminative stimuli present on the trial rather than (as in alternation) by stimulus events from the preceding trial.

In the spatial reversals procedure (Experiment 3), a variable number of trials on which a press on the left lever was reinforced alternated with a variable number of trials on which a press on the right lever was reinforced. All trials were signalled alike—by the simultaneous illumination of the two levers. The animals readily learned a "win-stay, lose-shift" strategy: press the same lever as on the preceding trial ("stay") if the response on the preceding trial had been reinforced, but "switch" to the opposite lever if the response on the preceding trial had not been reinforced.

Thus, the animal was required to "remember" over the intertrial interval the specific events from the preceding trial—which lever had been pressed and whether or not the press had been reinforced. A treatment which affected working memory should alter the accuracy of lever pressing. A treatment which non-specifically altered performance should change only the probability of response occurrence.

Four pesticides were examined in the present study: carbaryl (Sevin: 1-naphthyl N-methyl carbamate), propoxur (Baygon: 1-isopropoxyphenyl N-methyl carbamate), deltamethrin (a synthetic pyrethroid) and chlordimeform (a formamidine). The four reference drugs were scopolamine, methscopolamine, physostigmine and chlordiazepoxide. Considerable evidence implicates central cholinergic involvement in memory [2]; all of the above pesticides except chlordimeform affect cholinergic functioning. Carbaryl and propoxur inhibit acetylcholinesterase [3,5], deltamethrin has some cholinergic-like effects on behavior [13], whereas chlordimeform inhibits monoamine oxidase in addition to other pharmacological actions but does not inhibit acetylcholinesterase [11]. With regard to the reference drugs, physostigmine is a central and peripheral inhibitor of acetylcholinesterase, scopolamine has both central and peripheral anticholinergic action, and methscopolamine has almost exclusively peripheral anticholinergic effects. Chlordiazepoxide was included among the reference drugs because, like chlordimeform, it stimulates food intake, but unlike chlordimeform, it also stimulates water intake [19].

METHOD

Animals

The subjects were 28 male Sprague-Dawley derived (CD) rats received from Charles River Breeding Co. at approximately 70 days of age. Eight of these rats served in Experiment 1, 13 in Experiment 2, and 7 in Experiment 3. They were housed individually and maintained on a 12-hour light-dark cycle. The animals were maintained on Purina rat chow ad lib, but were deprived of water for approximately 23 hours prior to the 5-days-a-week experimental sessions. The animals received water as reinforcement during experimental sessions and also for approximately 20 min following each experimental session. Water was freely available on weekends.

Apparatus

The animals were trained and tested in two-lever operant chambers (25 × 24 × 18.5 cm) constructed at Indiana University. Two frosted glass levers, requiring 25–30 g force for activation, were mounted on the front wall of each chamber. The levers were 10 cm above the grid floor and displaced 6.5 cm on either side of the midline.

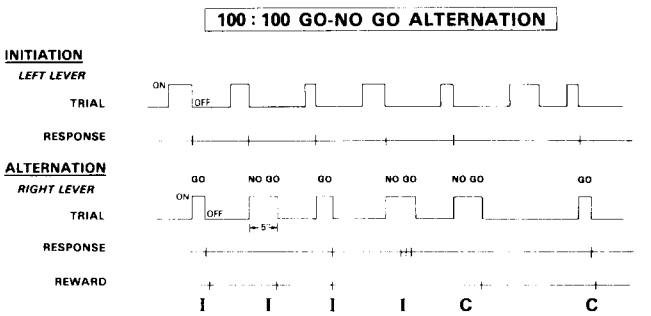

FIG. 1. Schematic representation of subject-initiated go-no go alternation procedure. I = initial (noncorrection) trials; C = correction trials.

A brass spout, calibrated to deliver 0.05 cc water/drop, protruded 2.7 cm into the chamber and was located 5.5 cm above the floor on the center line of the front panel. Three recessed white 6-W panel lights were mounted 15 cm above the floor, one over each lever and one on the center line. Each operant chamber was enclosed in a heavy, sound-attenuating shell. A Texas Instruments 980A minicomputer, located in a room adjoining the experimental room, controlled the experiments and recorded the data.

BEHAVIORAL PROCEDURES

Experiment 1: Go-No Go alternation

Only the right lever was accessible to the rat in Experiment 1: the left lever was always covered with a metal shield. The rats first received preliminary training in which they learned to press the lever, and then to press the lever during the 5-sec trials when the panel light was on. Alternation training began when the rats responded on more than about 80 percent of their trials and responding on the trials clearly exceeded responding on the intertrial intervals. In the alternation schedule, go trials, on which a lever press terminated the trial and produced water reinforcement, alternated with no go trials. All no go trials lasted for 5 sec. If the rat did not press the lever during the no go trial, reinforcement was delivered at the termination of the trial; if the rat did press the lever during the no go trial, the trial terminated without reinforcement. Correction trials followed all non-reinforced (incorrect) go and no go trials: performance on correction trials was not included in the calculation of response accuracies.

Accuracy of response was measured in terms of probability of response on initial (non-correction) go trials ("hits") and on initial (non-correction) no go trials ("false alarms"). (These two probabilities were also measures of correct alternations, since an initial go trial was defined by occurrence of a correct response on the immediately preceding no go trial and an initial no go trial was defined by occurrence of a correct response on the immediately proceding no go trial.) Experimental sessions lasted until 100 reinforcements had been delivered or 90 min had elapsed—whichever occurred first.

Experiment 2: Subject-initiated Go-No Go Discrimination and Alternation

The rats were first trained in a subject-initiated go-no

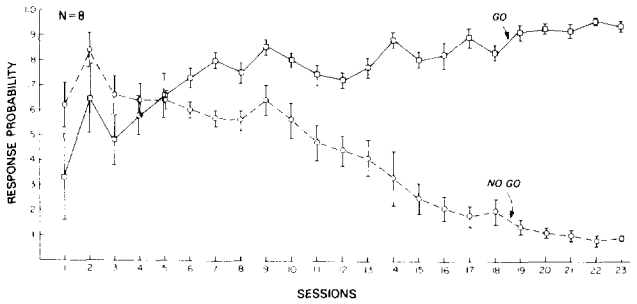

FIG. 2. Acquisition of go-no go alternation performance by the eight rats in Experiment 1 (automatic initiation of trials). Brackets indicate ± 1 S. E. M.

go discrimination procedure and tested with all eight of the toxicants and drugs. They were then retrained in the subject-initiated go-no go alternation procedure and retested with the same compounds (See Fig. 1).

a. Subject-initiated go-no go discrimination. Initiation trials, signalled by illumination of the left lever for a maximum of 5 sec, were presented on a variable time schedule of 2.5, 5, 10, and 20 sec between trials. A press on the left lever during the initiation trial, a "trial initiation response," terminated the lever light and produced a discrimination trial signalled by "bright" or "dim" illumination of the right panel light. The ratio of brightness between the "bright" and "dim" stimuli was approximately 56:1. The right panel light was illuminated for a maximum of 5 sec. For half of the animals, if the right panel light was "bright" (go trial) a press on the right lever terminated the discrimination trial and produced a drop of water, whereas if the right panel light was "dim" (no go trial) failure to press the right lever during the trial produced a drop of water at the end of the trial. (Pressing the right lever on a no go trial did not terminate the trial and did not produce water upon trial termination). For the other half of the animals, the "bright" and "dim" go and no go stimuli were reversed.

The "bright" and "dim" discriminative stimuli were presented in semi-random order following the trial initiation responses. Correction trials, in which the same discriminative stimulus was presented as on the immediately preceding trial, followed all non-reinforcement (i.e., incorrect) trials.

Over-all tendency to respond during a session was measured by the probability of response on initial (noncorrection) initiation trials, i.e., by the proportion of these trials on which the animal produced a discrimination trial. Accuracy of response on discrimination trials was measured in terms of the proportion of initial go trials and initial no-go trials on which the animal responded. Experimental sessions lasted until the animal had received 100 reinforcements or until 90 min had elapsed—whichever occurred first.

b. Subject-initiated go-no go alternation. The procedure was the same as in Experiment 1, except that the rats initiated their own trials. The initiation trials were presented at fixed intervals of 5 sec. Initiation (left lever) responses on the initiation trials produced alternation trials, signalled by illumination of the right panel light at the same intermediate brightness on all trials. Go trials, on which a right lever produced water and terminated the trial, alternated with no go trials on which failure to press the right lever on the

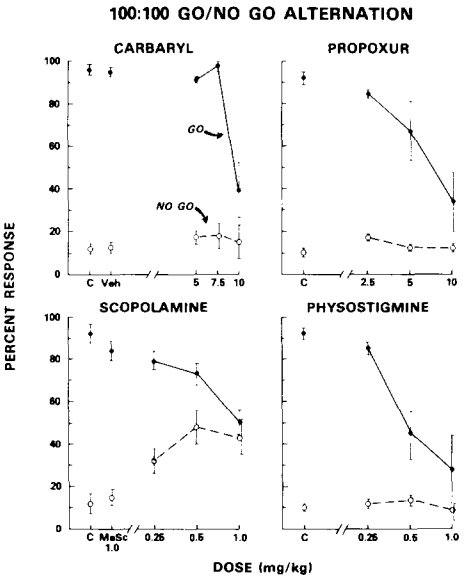

FIG. 3. Effects of two pesticides—carbaryl and propoxur—and two reference drugs—scopolamine and physostigmine—on baseline go-no go alternation performance in Experiment 1. C = control (no injection); Veh = vehicle, and MeSc = methyl scopolamine. Brackets indicate ± 1 S. E. M.

trial produced water upon trial termination. Correction trials followed all non-reinforced (incorrect) trials.

As in the discrimination procedure, over-all tendency to respond in the alternation procedure was measured by the proportion of initiation responses made on initial trials, that is, on the first initiation trial opportunity following a correct alternation trial. Accuracy of responding was measured in terms of probability of response on initial (noncorrection) go or no go alternation trials. The experimental session lasted until the animal had received 100 reinforcements or until 90 min had elapsed.

Experiment 3: Spatial Reversals (Lose-Shift)

The rats were first trained on a preliminary schedule in which discrete trials were signalled by illumination of either the left or the right lever light, in random order. The first response on either lever terminated the trial, but only responses on the illuminated lever produced the reinforcer. Correction trials followed all incorrect (non-reinforced) trials. Maximum trial duration was 5 sec; the intertrial interval was 4 sec plus a one-sec pretrial delay. Each lever press during the pre-trial delay period postponed onset of the next trial for one sec from the time of the lever press.

Training on the final spatial reversals schedule began when the animals were responding correctly on approximately 70 percent of the trials in the preliminary schedule. The spatial reversals trials were signalled by the simultaneous illumination of the left and right levers. As in the preliminary schedule the intertrial interval durations were 4 sec plus a one-sec pretrial delay. The animals were trained to perform in accordance with a "win-stay, lose-shift" strategy. Four types of trial were presented: initial (non-correction) stay trials, initial switch trials, stay correction trials, and switch correction trials. Initial stay trials immediately followed all trials on which a reinforced response had occurred: a

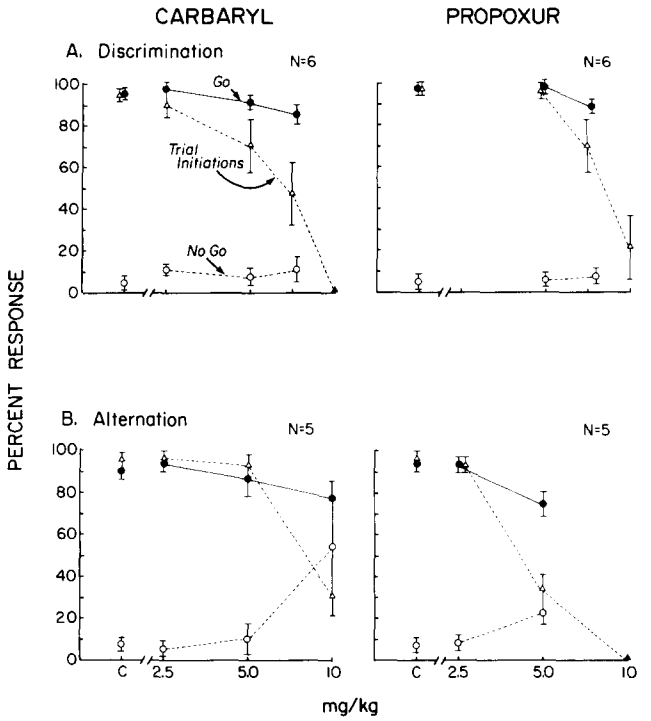

FIG. 4. Effects of carbaryl and propoxur on performance of a go-no go discrimination between a "bright" and "dim" panel light (top) and on go-no go alternation (bottom) in Experiment 2. The plotted curves show percentage of responses on initial go and no go trials ("accuracy") and percentage of trial initiations. Brackets indicate ± 1 S. E. M. Performance on go and no go trials was not plotted if percentage of trial initiations was less than 25%.

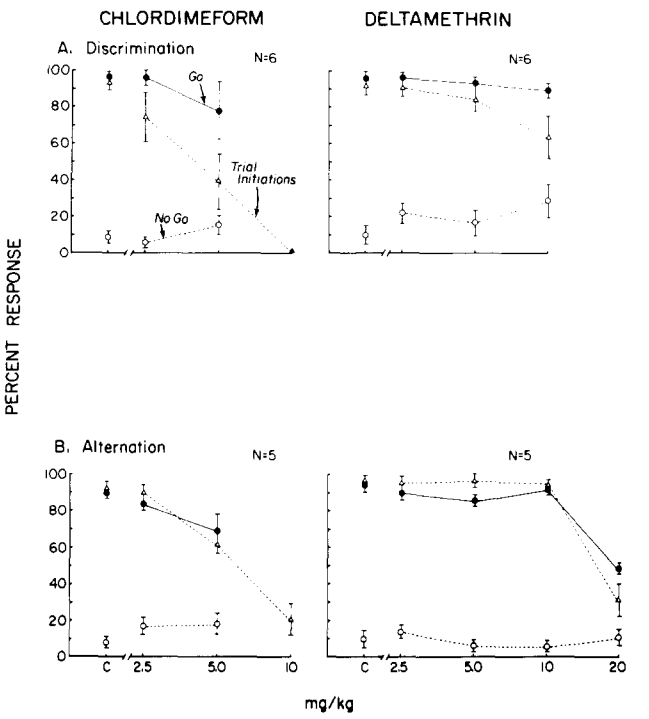

FIG. 5. Effects of chlordimeform and deltamethrin on go-no go discrimination and alternation performance in Experiment 2. Same notation as Fig. 3.

"stay" response (i.e., pressing the same lever as on the preceding trial) was always the "correct" response on stay trials. Initial switch trials immediately followed all trials upon which a correct stay response had *not* been reinforced. On switch trials, responses on the lever opposite from that pressed on the preceding trial were reinforced. Correction trials followed all trials on which the animal had either pressed the incorrect lever or had failed to respond.

One hundred stay trial "runs" were presented in the experimental session—50 runs of right lever trials and 50 runs of left lever trials. Each run consisted of one to seven initial stay trials and concluded with a non-reinforced stay trial which, in turn, was followed by an initial switch trial. There were 352 initial trials in a session—252 initial stay trials of which 152 were reinforced—and 100 initial switch trials. The number of runs of different run lengths was inversely related to run length, such that *given* a reinforced response on a trial, the conditional probability of reinforcement of a "stay" response on the next trial remained approximately 0.60, regardless of the number of prior trials in the run [1].

Accuracy of spatial reversal performance was measured in terms of the proportion of stay and switch responses on initial (non-correction) stay and initial switch trials, respectively. The overall tendency to respond was indicated by the proportion of response failure—the proportion of all initial and correction trials on which no response occurred. In the presentation of results, the accuracy measures—proportion of switch and stay responses—were not reported for treatment doses for which the percentage of response failures for 50% or more of the animals exceeded an arbitrary cut-off of 75%.

Pesticides and Drug Testing

In Experiment 1, each of eight rats was tested once with each dose of a range of doses of carbaryl, propoxur, scopolamine, and physostigmine. In Experiment 2 each of six rats was tested once in the discrimination and once in the alternation procedure with each dose of a range of doses of each of the four pesticides, and each of seven rats was tested once in each procedure with each dose of a range of doses of each of the four reference drugs. In Experiment 3, each of seven rats was tested once with each of the various doses of the pesticides and reference drugs. Treatments were given on Tuesdays and Fridays with control performance recorded on Mondays and Thursdays. The order of administration of the various doses of a compound was counterbalanced among the various animals that received that compound.

Compounds were administered by IP injection 20 min prior to the experimental session. Carbaryl, deltamethrin, and propoxur were dissolved in warm corn oil; all other compounds were dissolved in distilled water. The following compounds were generously donated by their manufacturers: carbaryl 99.9% analytical grade from Union Carbide, Jacksonville, FL; propoxur 97% technical grade from Mobay Chemical Corp., Kansas City, MO; chlordimeform 97%

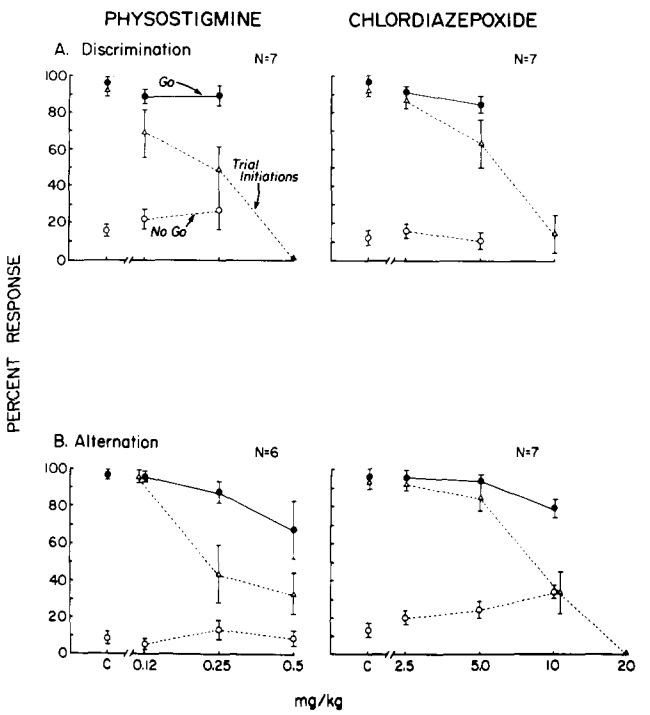

FIG. 6. Effects of physostigmine and chlordiazepoxide on go-no no discrimination and alternation performance in Experiment 2. Same notation as Fig. 3.

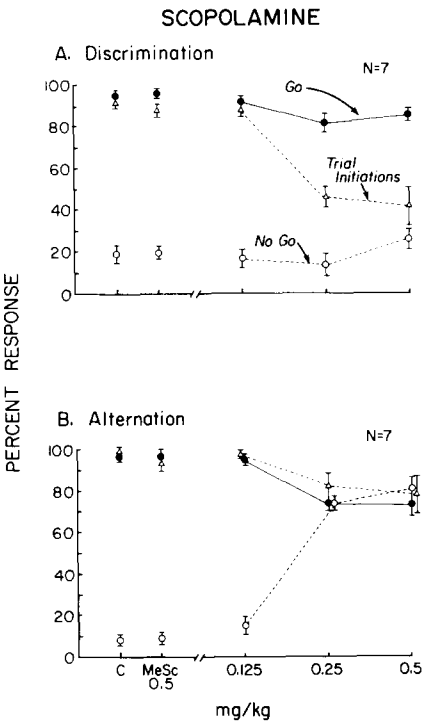

FIG. 7. Effects of scopolamine on go-no go discrimination and alternation performance in Experiment 2. Same notation as Fig. 3.

from Nor-Am, Napierville, IL; deltamethrin from Roussel UCLAF, Romainville, France, and chlordiazepoxide HCl from Hoffmann LaRoche, Inc., Nutley, NJ. Scopolamine hydrobromide, methyl scopolamine bromide, and physostigmine (eserine) were purchased from Sigma Chemical Co., St. Louis, MO.

RESULTS

Figure 2 shows acquisition of go-no go alternation performance in Experiment 1, where trials were presented automatically upon termination of the intertrial interval. The rats consistently responded on more than 90 percent of their initial go trials and on about 10 percent of their initial no go trials after about 20 training sessions. Figure 3 shows that carbaryl, propoxur, and physostigmine had qualitatively similar effects on this alternation performance: percent response on initial go trials declined rapidly as dose increased whereas the percent response on no go trials showed little change. In contrast, scopolamine, the cholinergic blocker, both lowered responding on go trials and markedly increased responding on no go trials.

The results of Experiment 2, in which the animals initiated their own alternation or discrimination trials, are presented in Figs. 4, 5, 6, and 7. No systematic relationships were observed between intertrial interval and performance on discrimination trials; hence results for the four intertrial intervals were combined. Except for scopolamine, the effects of the test compounds were qualitatively similar and effects of the compounds on discrimination performance were similar to their effects on alternation. As dose increased, percentage of trial initiations first decreased gradually and then abruptly. Accuracy, measured in terms of percent of responses on go and no go trials, typically remained high even at doses where percentage of trial initiations was drastically reduced. Accuracy of go and no go trial performance was not reliable when percentage of trial initiations fell below about 25 percent; however even under these circumstances accuracy of responding on go and no go trials remained well above chance. Effects of test substances on alternation accuracy in Experiment 2 were remarkably similar to their effects on alternation accuracy in Experiment 1 (cf. Fig. 3).

As previously indicated, effects of scopolamine differed markedly from those of the other compounds (see Fig. 7). Scopolamine affected alternation accuracy much more than discrimination accuracy. It dramatically increased responding on no go alternation trials: accuracy of alternation responding was drastically disrupted at the higher scopolamine doses even though proportion of trial initiations remained high.

A sampling of trial initiation latencies revealed no differences between mean latency of initiation of go and no go alternation trials, nor between the latencies on the discrimination trials following the four different intertrial intervals. No systematic changes in latency were noted following administration of the various pesticides.

Figures 8 and 9 show performance on spatial reversals

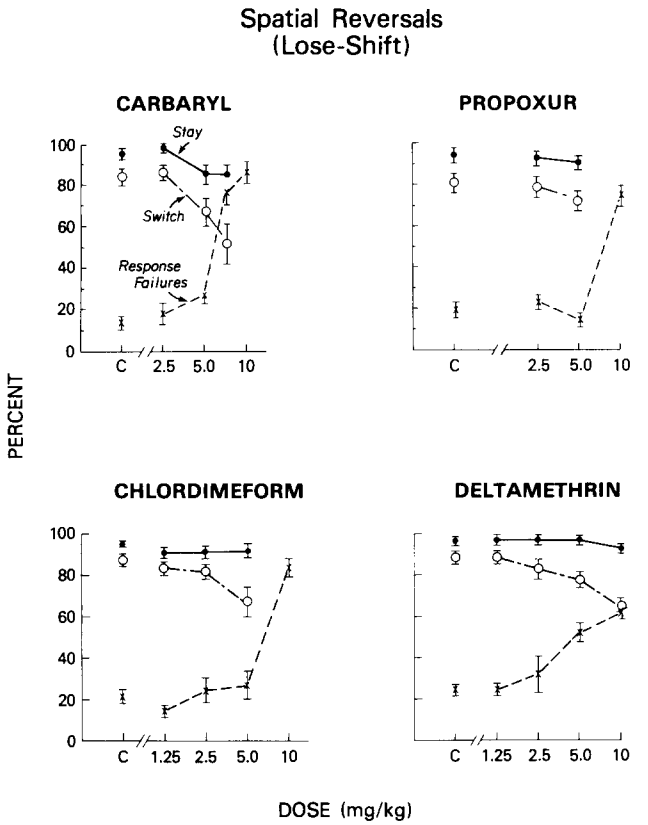

FIG. 8. Effects of the four pesticides on percentage of stay responses on initial stay trials, percentage of switch responses on initial switch trials, and on percentage of response failures. Accuracy of performance on switch and stay trials is not shown when percentage of response failures exceeded arbitrary limits (see text).

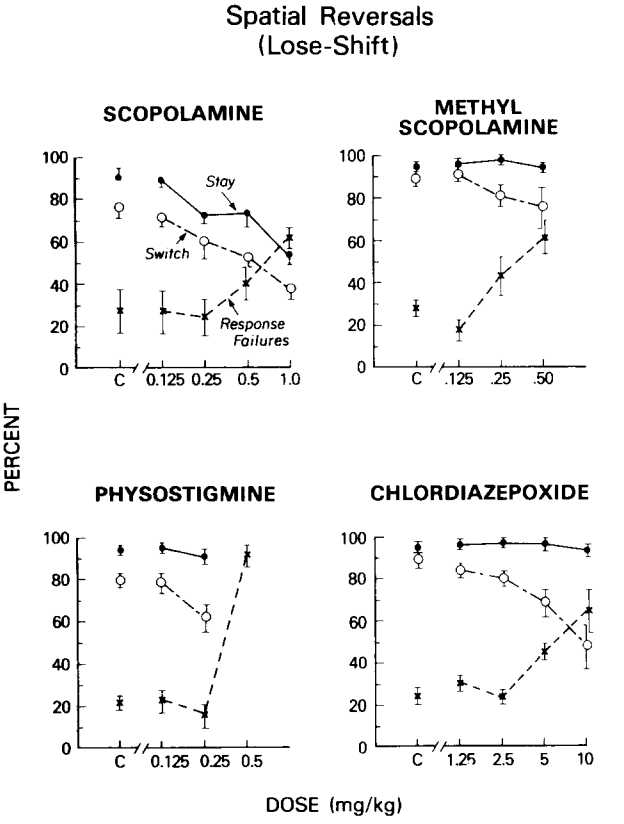

FIG. 9. Effects of the four reference drugs on percentage of stay responses on initial stay trials, percentage of switch responses on initial switch trials, and on percentage of response failures. Same notation as Fig. 7.

under control (non-treatment) conditions and following administration of the various test compounds. Under control conditions, accuracy of performance on both initial stay and switch trials typically exceeded 80%, and the animals responded on more than 70% of their trials. Stay trial accuracy was always greater than switch trial performance, presumably because of the 60:40 ratio of stay to switch trials (accuracy of performance on the two types of trials did not differ in an exploratory study where the ratio of stay to switch trials was 50:50). The accuracy of switch and stay performance did not vary with run length, i.e., with the number of immediately preceding stay trials.

Figures 8 and 9 show that the pesticides, with the possible exception of deltamethrin, had qualitatively similar effects on spatial reversals performance. As dosage increased, overall accuracy at first declined moderately, due principally to a selective decrease in switch accuracy. At still higher doses, response failures increased abruptly. It is not possible to tell from the present data whether the qualitative effects of deltamethrin were like those of the other pesticides since a high dosage of deltamethrin (20 mg/kg) was not given.

In contrast, chlordiazepoxide and scopolamine substantially decreased accuracy at doses at which the animals continued to respond. Equal doses of scopolamine and methyl scopolamine produced similar percentages of response failures; however scopolamine had greater effects than methyl scopolamine on accuracy.

GENERAL DISCUSSION

The pesticides and physostigmine affected performance similarly in the three working memory procedures: they non-selectively and abruptly decreased responding with increasing dosage. This effect was manifested in the go-no go alternation procedures by the sharp decline in the dose-response curves for responding on "go trials" and for trial initiations; and in spatial reversals by the rapid increase in response failures on trials.

Table 1 compares the effectiveness of the pesticides and physostigmine in the various procedures. In spite of the diversity of measures of effectiveness employed, generally similar effective doses were obtained for each compound in the various procedures.

The pesticides and physostigmine did not specifically affect working memory. In Experiment 2 these compounds disrupted discrimination performance, in which the behavior was controlled by stimuli present on the trial ("reference memory"), as much as they disrupted alternation performance, in which the behavior was controlled by stimuli from preceding trials ("working memory"). No substantial reduction in accuracy of either alternation or spatial reversals performance was observed until proportion of trial initiation or response failures had fallen to low levels. These findings are consistent with the report [14] that rats treated with propoxur or carbaryl maintained their customary locomotor

TABLE 1

EFFECTS OF PESTICIDES AND PHYSOSTIGMINE ON PERFORMANCE IN WORKING MEMORY AND DISCRIMINATION PROCEDURES

Procedure		Measure	Dose - mg/kg				
			Carbaryl	Propoxur	Chlordimeform	Deltamethrin	Physostigmine
Experiment 1	Go-No Go Alternation	50% reduction in go trial responses	9	7.5			0.5
Experiment 2	Subject-initiated:						
	1) go-no go alternation	50% reduction in trial initiations	7.5	4	6	17	0.25
	2) discrimination	50% reduction in trial initiations	7	8	4	>10	0.25
Experiment 3	Spatial Reversals	50% response failures	7	9	8	10	0.4

patterns in a figure-8 maze even at doses that greatly reduced over-all activity.

In contrast, scopolamine, an alleged amnesic agent [10] did impair working memory in these procedures. In Experiment 2, scopolamine disrupted alternation performance much more than discrimination performance. Furthermore, it disrupted alternation performance (principally by increasing responding on no go trials) at doses that only moderately decreased the proportion of trial initiations. Baseline discrimination and alternation accuracies were approximately equivalent: hence scopolamine's differential effect on alternation and discrimination was not due to differences in level of stimulus control [8]. Presumably, scopolamine affected alternation accuracy more than discrimination accuracy because intact working memory was required for accurate alternation performance but not for accurate discrimination performance. This interpretation is supported by the recent demonstration that scopolamine selectively disrupts working memory, but not reference memory, in the radial maze [18].

In spatial reversals, also, the animals continued to respond on a substantial proportion of their trials following doses of scopolamine that reduced accuracy of responding on switch and stay trials nearly to chance levels. This effect of scopolamine on spatial reversals performance was quantitatively and qualitatively consistent with its impairment of accuracy of entry into new arms in the somewhat analogous radial maze [4,18].

In conclusion, this report has described the type of behavioral studies required to determine whether a behavioral effect constitutes an effect on working memory. The present studies indicate that, contrary to common belief that toxicants impair memory [12], four representative pesticides (carbaryl, propoxur, chlordimeform, and deltamethrin) do not specifically impair working memory, but rather have nonspecific behavioral suppressant effects.

ACKNOWLEDGEMENT

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