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Kinetics and Thresholds of Several Indices of Lindane-Induced Toxicity[1]

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WOOLLEY, D. E. AND J. A. GRIFFITH. *Kinetics and thresholds of several indices of lindane-induced toxicity.* PHARMACOL BIOCHEM BEHAV **33**(4) 787–792, 1989.—The effects of lindane, administered either IP (4, 6 or 8 mg/kg in dimethylsulfoxide, 0.5 ml/kg) or PO (30, 40 or 50 mg/kg in oil, 1 ml/kg), were compared in male rats. Effects appeared later and lasted longer after PO administration. After either route, convulsant effects occurred first and were over before hypothermic effects were maximal. Also, hypothermia subsided before hypophagia ended. After IP administration, hypothermia had the lowest threshold and convulsions the next lowest; reduced food intake was produced only by the highest dose, which also produced 43% deaths. By contrast, after PO administration, all doses reduced food intake and produced hypothermia, but deaths did not occur after even the highest dose. The different time courses and thresholds for the different indices of toxicity suggest that different target sites or mechanisms may be involved. Thus, effects on the gut, in addition to effects on the brain, may account for the longer duration and greater sensitivity of reduced food intake, compared to lethal and hypothermic effects, after PO administration of lindane. After administration of lindane IP, peripheral vasodilation (as demonstrated by an increase in tail temperature) preceded colonic hypothermia. This could be explained if lindane inappropriately activated heat-loss mechanisms.

Convulsions Food intake GABA Lindane Temperature regulation

LINDANE, the gamma isomer of hexachlorocyclohexane, continues to be used to treat ectoparasites in both human and veterinary medicine (20,23). Although it produces a constellation of toxic effects, it is known primarily for its convulsant actions. However, this laboratory has previously reported that a single administration of lindane in oil PO in the rat also produces profound anorexia, hypothermia and long-term enhancement of the prepyriform-evoked potential recorded in the dentate gyrus (8, 9, 31–34). Lindane's primary mechanism of action is at the synapse where it has been shown to increase neurotransmitter release, perhaps by increasing calcium entry [reviewed by (10,33)]. It is also believed to exert antiGABAergic effects via an action at the picrotoxinin (PTX)/t-butylbicyclophosphorothionate (TBPS) site on the $GABA_A$-activated chloride channel (1, 12, 14) and to inhibit GABA-activated chloride flux (2, 3, 5, 7, 17). Administration of agents which enhance GABAergic activity, such as diazepam, clonazepam or phenobarbital, prevented lindane-induced convulsions, anorexia and hypothermia (8, 9, 32, 33). Administration of Ro 5-4864, an atypical benzodiazepine which is a ligand for the "peripheral" benzodiazepine receptor (22) and, in addition, has antiGABAergic activity via an action at the PTX/TBPS site (6, 16, 26, 29), exacerbated the toxicity of lindane (8,9).

We had previously reported that hypothermia and anorexia last longer and have a lower threshold than do convulsions after a single dose of lindane PO (8,9). Similarly, we had reported that a single dose of lindane IP (5 mg/kg) produced hypothermia but not convulsions (32). An objective of the present studies was to clarify further the time course and relative degree of effects for several of the indices of lindane-induced toxicity, i.e., hypothermia, anorexia and convulsions, particularly as influenced by route of administration. The relative order of thresholds for these toxic effects should not vary with route of administration if the primary target tissue is the same for each, e.g., the central nervous system (CNS). On the other hand, because GABA and receptors for GABA have been found in the gastrointestinal (GI) tract [for review, see (9,25)], it seemed possible that anorexia, after an oral administration of lindane, might be due to a direct effect on the GI tract, as well as on the CNS.

Another objective was to compare the time course of peripheral vasodilation or constriction, as measured by changes in tail surface temperature, simultaneously with changes in core (i.e., colonic) temperature, in order to learn more about the mechanisms involved in lindane-induced hypothermia.

METHOD

General Procedures

Adult Sprague-Dawley rats (bred from animals obtained from Simonsen's Laboratories, Gilroy, CA) were housed individually in stainless steel hanging cages in a temperature-controlled room (23 ± 0.5°C) under controlled lighting (14 L:10 D). In Experi-

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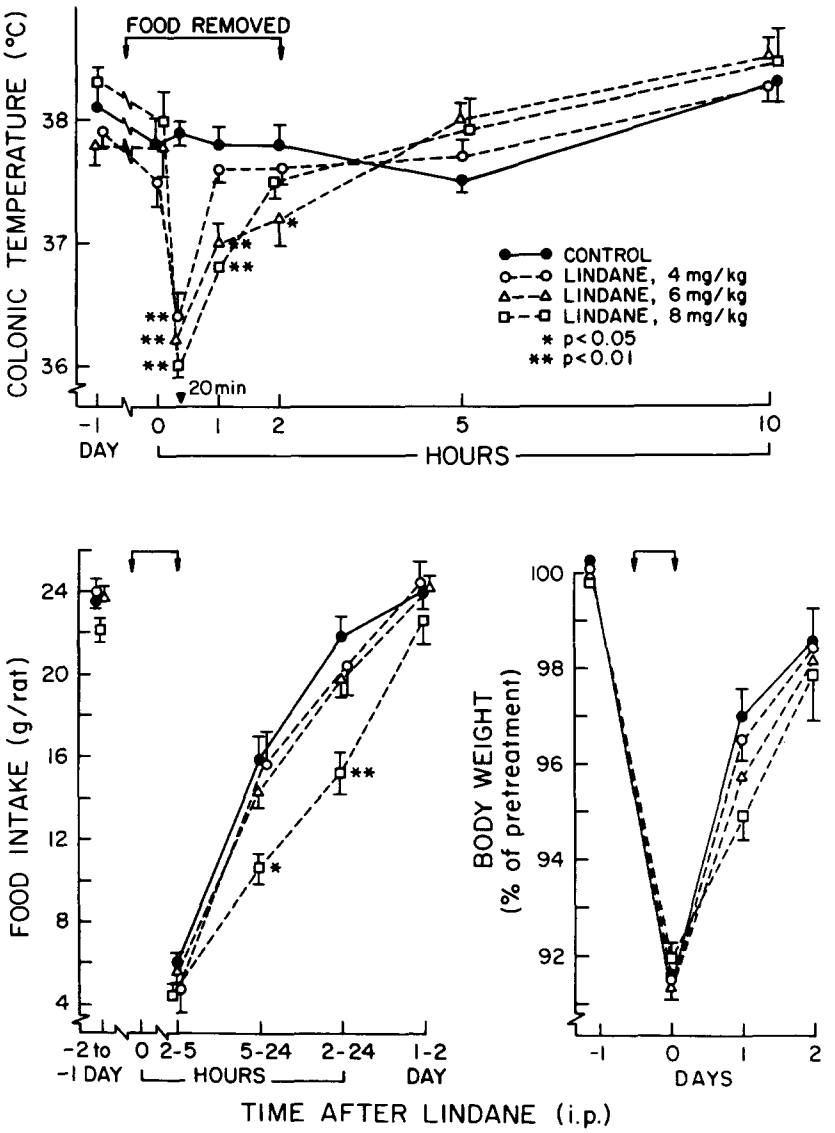

FIG. 1. Changes in colonic temperature, food intake, and body weight with time after IP administration of a single dose (4, 6 or 8 mg/kg) of lindane in DMSO in male rats. Controls received only the vehicle. Food intake for the interval 2 to 24 hr is the sum of food intake for the 2 to 5 and 5 to 24 hr periods. Vertical bracketed lines represent SEMs.

ments 1 and 2, rats were allowed free access to water and to ground rodent chow (Purina 5001; St. Louis, MO), except when the chow was removed the night before dosing. Measurements of food intake, body weight, and colonic temperature were made daily for several days prior to administration of lindane or vehicle to assure that they were stable. For measurements of food intake, unaccounted spillage of food was minimized by using food cups centered and glued to the inside of larger metal containers. Colonic temperatures were measured with a rectal thermistor probe connected to a telethermometer (Yellow Springs Instrument, model 42SC; Yellow Springs, OH). In Experiment 3, for tail skin temperatures, a disk thermistor probe was used with a small amount of electrode paste on the probe to help increase thermal contact with the skin.

In the first two experiments to compare IP versus PO effects, lindane or the vehicle was administered an hour following "zero hour" measurements of colonic temperature and body weights on the morning after fasting. Rats were observed for the appearance of convulsions for at least 2 hr following administration, by which time seizure activity had disappeared. After dosing, temperatures, food intake and body weights were measured at the times indicated in the Results section or in the appropriate figures. Food cups were returned following temperature measurements 2 hr after dosing in Experiment 1 and immediately following temperature measurements 15 min after dosing in Experiment 2.

For IP administration, lindane (Sigma Chemical Co., St. Louis, MO) was dissolved in dimethylsulfoxide (DMSO; Crown Zellerbach Corp., Camas, WA) and injected in a volume of 0.5 ml/kg body weight. For PO administration, lindane was dissolved in oil and administered by gastric intubation in a volume of 1 ml/kg body weight. Controls received the appropriate vehicle. In Experiments 1 and 2, dosing and measurements were made on one

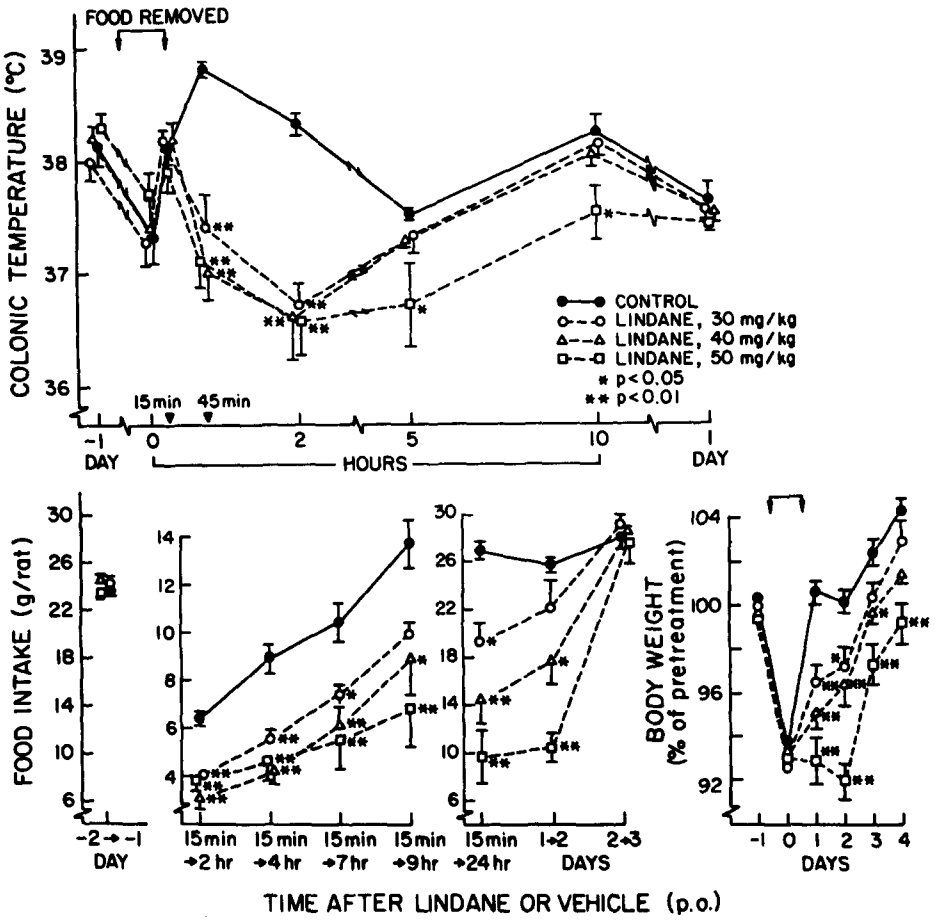

FIG. 2. Changes in colonic temperature, food intake, and body weight with time after PO administration of a single dose (30, 40 or 50 mg/kg) of lindane in oil in male rats. Missing S.E. bars are smaller than the symbols for the group mean.

rat from each group before proceeding to the second rat from each group, etc.

Experimental Protocols

In Experiment 1, 28 adult male rats were divided into 4 equal groups. After the zero hour measurements, animals were injected IP with either 4, 6 or 8 mg/kg lindane or the DMSO vehicle (controls).

In Experiment 2, 30 adult males rats were divided into 4 groups of 7 or 8 rats each. After the zero hour measurements, animals were intubated with either 30, 40, or 50 mg/kg lindane or the oil vehicle (controls). These doses were based on a previous finding from this laboratory that 30 mg/kg of lindane in oil PO did not produce hypothermia, but did produce long-term potentiation of a limbic-evoked potential in fed female rats (32–34), whereas 40 mg/kg was an effective dose to produce hypothermia and anorexia in fasted female rats (9, 32, 33).

In Experiment 3, six nonfasted adult female rats were used to determine the time course of the effects of lindane (12 mg/kg) administered IP in DMSO on tail skin and colonic temperatures. In order to determine if tail surface temperature varied at different positions along the tail, temperatures were measured at two different positions: one at the base of the tail and the other two inches from the base. To assure reproducibility in positioning the probe at the same site on the tail, two recording locations on the top of the tail were marked with an indelible ink pen. Animals served as their own controls and were injected first with either lindane or the vehicle and then a week later with the other agent.

Statistical Analysis

When the significance of differences between the means of treated and control groups was determined, analysis of variance (ANOVA) was conducted first. When the overall F ratio was significant at the $p<0.05$ level, Fisher's Least Significant Difference (LSD) test was used as the post hoc test, with the level of significance corrected for the number of comparisons by the Bonferroni method (15).

RESULTS

Experiment 1. Dose-Response Effects of Lindane Administered IP in Male Rats (Fig. 1)

Convulsions were not observed in the group receiving the lowest dose, but were observed in five or six of seven rats in the groups receiving the middle or highest doses, respectively. Time to first convulsion (mean ± SE) was 6.4 ± 0.9 min in the group

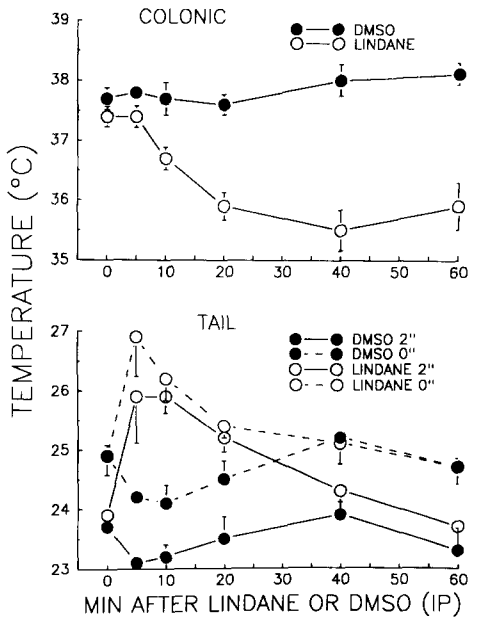

FIG. 3. Comparison of the changes in colonic and tail surface temperatures with time after IP administration of a single dose (12 mg/kg) of lindane in DMSO in female rats. Tail surface temperatures were measured both at the base, zero inches (0") from the body, and 2 inches (2") from the body.

receiving the middle dose and 3.8 ± 1.0 min in the group receiving the highest dose. Seizures were no longer observed in either group by 15 min after dosing. Convulsions consisted primarily of myoclonic (whole body) jerks, forelimb clonus, and head clonus. Two rats in both the middle and highest dosage groups exhibited tonic forelimb extension and two rats receiving the highest dose also exhibited severe hopping seizures. In the group receiving the highest dose, three deaths (43%) occurred between 15 and 43 min after dosing. No other deaths occurred.

By 20 min after dosing, colonic temperatures had fallen from pretreatment values by (mean ± S.E.) 1.1 ± 0.3, 1.6 ± 0.3 and 2.0 ± 0.3°C, in the lowest, middle, and highest dosage groups, respectively. Thus, the lowest dose, which was subconvulsant, still produced hypothermia. Temperatures had returned to normal by 1 hr in the group receiving the lowest dose, by 5 hr in the group receiving the middle dose, and by 2 hr in the group receiving the highest dose (presumably because three of the most seriously affected rats of this group had died by this time).

Reduction in food intake occurred only in the group receiving the highest dose of lindane and was not evident in the 2–5 hr period after dosing but was present in the 5–24 hr period, when temperatures had returned to normal. A trend towards slower recovery of body weight one day after dosing appeared to be dose-related but did not reach statistical significance.

In summary, after IP administration, the lowest dose (4 mg/kg) only produced hypothermia. At a dose 50% higher (6 mg/kg), 71% of the rats showed seizures as well. At a dose 100% higher (8 mg/kg), in addition to hypothermia, 86% of the rats showed seizures, 43% died, and food intake was reduced. (Two out of 2 deaths occurred at 10 mg/kg just prior to the start of the study, supporting the probability that 8 mg/kg was close to the LD_{50} in these animals.)

Experiment 2. Dose-Response Effects of Lindane Administered PO in Male Rats (Fig. 2)

When 30, 40, or 50 mg/kg lindane in oil was administered PO, all 7 rats in the highest dosage group and 3 of 7 rats in the middle and lowest dosage groups exhibited convulsions. Average time to first seizure for the 3 groups (from highest to lowest dosage) was 39, 38 and 48 min, respectively. Seizure activity was over by 1 hr in the 2 lower dosage groups and by 1.5 hr in the highest dosage group. Myoclonus was observed in all experimental groups, whereas hopping seizures and forelimb extension were observed in only 3 rats in the highest dosage group. No deaths occurred.

Colonic temperatures were lower after fasting and prior to dosing than in the pretreatment period but returned to normal 15 min after dosing (Fig. 2). Temperatures were 0.5 to 1.5°C lower in the lindane-treated groups than in controls at 45 min, were even lower at 2 hr, and had recovered by 5 hr after dosing in the lowest and middle dosage groups and by day 1 in the highest dosage group.

Dose-dependent effects of lindane in reducing food intake were observed for days 1 and 2 after dosing and on body weights for 2–4 days.

Experiment 3. Time Course of Changes in Tail and Colonic Temperatures After Lindane IP in Female Rats (Fig. 3)

Temperatures on the surface of the tail were significantly increased 5 min after IP administration of lindane when colonic temperatures had not yet changed, were maximally increased 5–10 min after administration, and had recovered by 40 min when colonic temperatures were maximally decreased. Though colonic temperatures had not yet changed 5 min after administration of lindane, they were decreased at 10 min and were decreased even more at 20, 40 and 60 min. Before administration of either lindane or vehicle, temperatures at the base of the tail were higher than temperatures 2 inches away, as would be expected if vasoconstriction were greater farther out along the tail than at the base. Five to 20 min after lindane, temperatures at the base and 2 inches away were the same, because temperatures at 2 inches had increased more than temperatures at the base.

After administration of the DMSO vehicle, colonic temperatures were not changed but tail temperatures were decreased slightly at 5–10 min. This could be explained if stress induced peripheral vasoconstriction.

DISCUSSION

Comparison of Time Course and Thresholds of Indices of Toxicity After IP Versus PO Administration of Lindane

After administration of lindane, seizures began and ended sooner than did either hypothermia or hypophagia, and hypothermia began and ended sooner than did hypophagia. The threshold for seizures was clearly higher than that for hypothermia after IP administration in the present study, as our preliminary reports had suggested (8,32). Similarly, Camon *et al.* (4) found that a subconvulsant dose of lindane produced a small decrease in colonic temperature 5 hr (the only time point examined) after PO administration.

The relative thresholds for lindane-induced hypothermia and hypophagia depended on the route of administration. After IP administration in DMSO, hypothermia occurred at each of the 3 doses, whereas food intake was reduced only by the highest dose which also produced 43 percent deaths. After PO administration in oil, even the highest dose did not produce deaths, but food intake and colonic temperatures were reduced by each of the 3 doses. Food intake was reduced for 1–2 days, whereas colonic temperature was reduced for only 2–10 hr. Thus, PO administration was

more effective than IP administration in reducing food intake, relative to effectiveness in producing either hypothermia or deaths.

The different time courses and thresholds for the various effects of lindane present some insight into the mechanisms involved. If the different time courses depended only on different concentrations of lindane within the same target site, e.g., one specific brain area, then it is difficult to see how convulsant effects could both appear first, as if they required the lowest brain concentration, and also be over before either hypothermic or hypophagic effects reached their peak. Postseizure depression is unlikely to account for the short time course of seizures because in most cases the seizures were too minimal to elicit such mechanisms. Since it is likely that the different effects of lindane are mediated via different target sites, perhaps each has a different pattern of uptake and release of lindane. The disappearance of lindane from rat brain was recently found to be biphasic with average half-times of 30 min and 3 days (18). The shorter half-time for release could readily correspond to the more rapid recovery from seizures than from the other toxic effects. The shorter and longer half-times (18) may represent disappearance from gray and white matter, respectively; uptake and release of p,p'-DDT [1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane] has been found to be faster for gray matter than for white matter and signs of poisoning correlated with concentrations in gray matter [reviewed by (30)]. For comparison, uptake of radiolabelled lindane 30 min after IV administration did not differ very much among 15 or more brain areas, which appeared to consist primarily of gray matter, though uptake was higher in corpus callosum (21) which is white matter.

Effects on the gut, as well as on the brain, could explain the relatively greater effectiveness of lindane in reducing food intake when administered PO than when given IP. Also, after IP administration, the relatively long time to onset of hypophagia, compared to the time to onset of hypothermia, may reflect the time required for redistribution of lindane from intraperitoneal fat to gut. Another possibility is that lindane interfered with the food intake mechanisms normally activated at the time lights go off, 10 hr after lindane administration [also see (9)].

Lindane may set in motion some effects which outlast its presence in a tissue. As an example, lindane administered to mice resulted in inhibition of sodium/potassium ATPase activity in synaptosomes 18 hr later, even though neither lindane nor its metabolites were present in the synaptosomes at this time (13). In addition, other work from this laboratory has shown that lindane (30 mg/kg PO) increased the amplitude of the evoked potential elicited in the hippocampal formation by stimulation of the prepyriform cortex for as long as 12–14 days in some rats (32–34), i.e., longer than the reported half-lifes of lindane in brain which have been demonstrated to be 30 min and 3 days (18), 1.5 days (27,28) or less than 24 hr (11).

Whatever the target sites, enhancing GABAergic activity with clonazepam or diazepam effectively antagonized the convulsant, hypothermic and anorexic effects of lindane (8, 9, 32, 33).

The Greater Effectiveness of IP Versus PO Administration in the Present Study

The considerably lower effective doses for seizures, hypothermia and death when lindane was given IP in DMSO rather than PO in oil may be explained by the much more rapid absorption of lindane after IP administration than after PO administration. The more rapid absorption would permit lindane to enter brain before it was metabolically degraded, excreted, or transported to such nontarget tissues as fat. Rapid absorption after IP administration, in turn, may be attributed to the DMSO vehicle, which is both hydrophilic and lipophilic and permits lipid soluble chemicals like lindane to penetrate the water phase of the peritoneal cavity more effectively. Also, only a small volume was administered per unit body weight, i.e., 0.5 ml/kg. By comparison, no deaths occurred in 25 rats after IP administration of 150 mg/kg lindane in oil in a volume of 5 ml/kg (27). Oil is an effective vehicle for PO administration since there are lipid transport mechanisms across the gut.

Time Course of Lindane-Induced Changes in Tail and Colonic Temperatures

The tail plays a significant role in temperature regulation in the rat; up to 20 percent of the heat produced by the animal can be lost via vasodilation of the tail (19). Also, tail temperatures can change very quickly in response to rapid changes in vasoconstriction or dilation of vessels in the tail, whereas changes in core temperature cannot change as rapidly because of the large mass of the body involved. Thus, 5 min after IP administration of lindane, tail temperatures had increased 2 degrees, but core temperature had not yet changed. The fact that increased tail temperature preceded the drop in colonic temperature suggests that the decreased core temperature resulted from peripheral vasodilation after administration of lindane.

The present observations could be explained if lindane inappropriately activated central heat-loss mechanisms. This would result in peripheral vasodilation first, followed by a decrease in core temperature as heat was dissipated. It is also theoretically possible that lindane may have acted directly on blood vessels to cause dilation, which, in turn, would have caused heat loss and the ensuing drop in core temperature. However, to our knowledge, there is no evidence that lindane does cause vasodilation by a direct aciton on vessels. Other antiGABAergic agents, such as picrotoxin and Ro 5-4864, also cause colonic hypothermia in a manner similar to that produced by lindane (31), suggesting that the hypothermic effects of these 3 agents have in common their antiGABAergic action.

The effects of lindane on surface versus core temperatures provide an interesting contrast to the effects of p,p'-DDT, described by this laboratory [reviewed by (30)]. DDT also increased tail temperature before colonic temperature changed. Next, however, tail temperature fell and colonic temperature rose to excessively high levels (40–42°C), just prior to death. This sequence could be interpreted to mean that tail temperature increased appropriately initially to prevent an increase in core temperature. When temperature regulating mechanisms failed near death, tail temperature dropped and core temperature rose, presumably because of excessive heat production which could no longer be dissipated. During this time, skin temperature of the back changed very little, suggesting that this area contributes little to heat dissipation, presumably because of the low thermal conductance of hair.

The different effects of DDT and lindane on body temperature emphasize the differences in the toxic effects of tremorogenic versus convulsant organochlorine insecticides. DDT is primarily tremorogenic, produces hyperthermia and is believed to act at voltage-sensitive sodium channels [reviewed by (30)]; lindane is primarily convulsant, produces hypothermia and is believed to act at the picrotoxinin site of the $GABA_A$-activated chloride channel (see Introduction).

Sex Difference in the Response to Lindane

After IP administration of 8 mg/kg, 3 of 7 male rats died in Experiment 1, whereas none of the 6 female rats injected IP with 12 mg/kg died in Experiment 3. This suggests that male rats are

much more sensitive than females to the toxic effects of lindane administration. However, the experiments were not done at the same time, nor with animals arriving in the laboratory at the same time, and, therefore, on the basis of the present work alone, this conclusion cannot be made with confidence. However, other work in this laboratory has confirmed that, indeed, male rats are more sensitive than females to the indices of lindane-induced toxicity measured here following either IP or PO administration [(31); Drummer and Woolley, unpublished observations]. Interestingly, when brain concentrations of lindane at appearance of first generalized seizure after IV administration were compared, female rats were slightly more sensitive to lindane (18).

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