Fate of Insecticides Administered Endotracheally to Rats[1]

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The evaluation of the fate of insecticides in animals has been classically determined after oral, dermal, and/or intraperitoneal administration of the compounds. Little information is available on the metabolic fate of these chemicals when inhaled, although inhalation toxicity studies are commonly conducted on products being developed for commercial use. The chemical and biological fate of inhaled insecticides could greatly influence their toxicity to animals, and a knowledge of their fate would be useful in estimating the potential hazards of these toxicants following exposure by inhalation.

In the present study, insecticides were quantitatively administered as aerosols to the lungs of rats via the trachea. The relative rates of absorption by the blood and the fate of the insecticides in the animals were determined.

MATERIALS AND METHODS

Insecticides. Four ^{14}C-labeled insecticides were selected for this study: carbaryl [1-naphthyl-^{14}C N-methylcarbamate (6,600 dpm/ug) and the carbonyl-^{14}C form (4,400 dpm/ug)], leptophos [O-methyl O-4-bromo-2,5-dichlorophenyl-^{14}C phenylphosphonothioate (7,800 dpm/ug) and O-methyl O-4-bromo-2,5-dichlorophenyl phenyl-^{14}C-phosphonothioate (8,000 dpm/ug)], parathion [(O,O-diethyl O-p-nitrophenyl-2,6-^{14}C phosphorothioate (13,600 dpm/ug) and the diethyl-^{14}C form (13,000 dpm/ug)] and chlordane-^{14}C (11,500 dpm/ug).

Treatment. Female Sprague-Dawley rats weighing approximately 200 g each were surgically prepared for treatment using techniques previously described (ATALLAH and DOROUGH 1975, BURTON and SHANKER 1974). Each animal was anesthetized with 13 mg of sodium pentobarbital, IP, which immobilized them for the duration of the experiment. A cannula was inserted between the fourth and fifth

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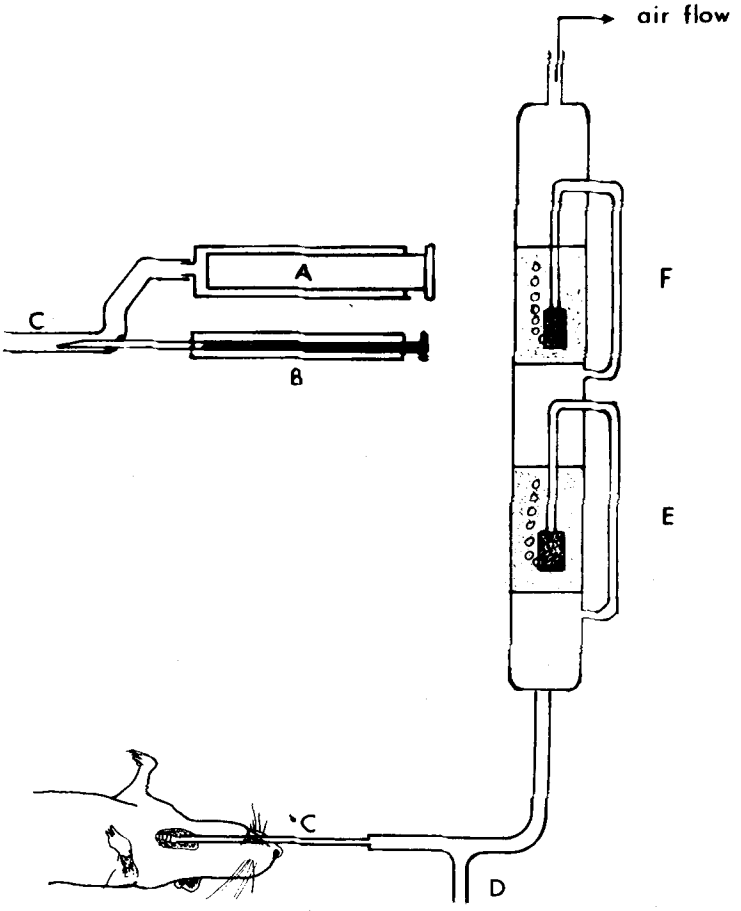
tracheal ring below the thyroid cartilage through which the insecticide solution was administered (Fig. 1).

FIGURE 1.



Method for delivery of ^{14}C-insecticides contained in 20 ul of ethanol to the rat lung via the trachea and collection of exhaled radiocarbon. (A) 5 ml syringe with air only; (B) 50 ul syringe with insecticide solution; (C) polypropylene tracheal tube; (D) inlet for air to animal and to vacuum source; (E,F) cold solvent and/or CO_2 traps.

The radiolabeled insecticide in 20 ul of ethanol was delivered to the lungs as an aerosol by depressing the plungers of the 50-ul

and 5-ml syringe simultaneously. Thus, the insecticidal aerosol was delivered to the lungs in a total air volume of 5 ml, held for 15 sec. to achieve maximum retention, and then the cannula leading from the trachea connected to a carbon dioxide trap (2:1 solution of 2-methoxyethanol and 2-aminoethanol). Blood samples were taken from the tail periodically for one hour and the animals then sacrificed and tissue samples collected for analysis.

Blood and Tissue Analysis. The blood, 0.2-0.4 ml, and tissue samples, 400-800 mg, were placed in quartz vessels and combusted in a Beckman Biological Materials Oxidizer. The radiocarbon generated as $^{14}CO_2$ during combustion was trapped and an aliquot of the solution radioassayed by liquid scintillation counting (Packard Model 3380/544).

Excretion Studies. Carbaryl-ring-^{14}C, leptophos-phenoxy-^{14}C, parathion-phenyl-^{14}C, and chlordane-^{14}C were administered to female rats in the manner described above. In this case, however, ether was used as the anesthetic and the incision closed immediately after administration of the insecticides. The animals were placed in plexyglass metabolism cages and the excreta monitored periodically for radiocarbon until excretion of radioactivity had ceased.

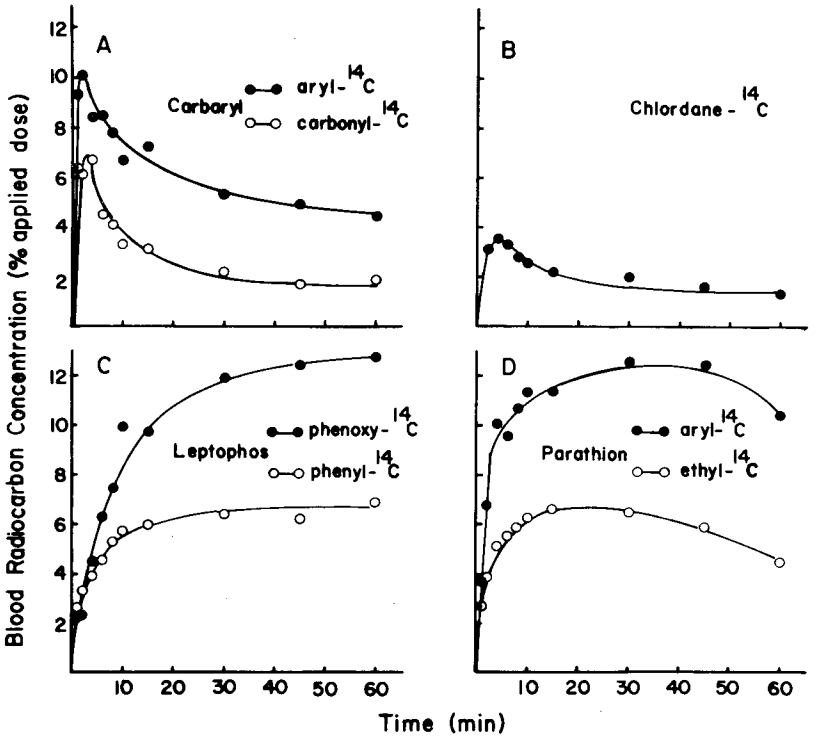
RESULTS AND DISCUSSION

Administration of the dose to the rats via the trachea resulted in quantitative retention of the inhaled insecticides. None of the intact insecticides was detected in the exhaled air. In fact, the only radiocarbon exhaled at all was ^{14}C-carbon dioxide, 2.5% of the applied dose, from animals treated with ^{14}C-carbonyl-labeled carbaryl.

^{14}C-Insecticide equivalents in the blood of rats during a one-hour period following treatment are shown in Fig. 2. Carbaryl-^{14}C (Fig. 2,A) and chlordane-^{14}C (Fig. 2,B) residues appeared rapidly in the blood with maximum concentrations occuring after only 2 to 5 minutes. Then, the residues immediately began to dissipate from the blood. Leptophos (Fig. 2,C) and parathion (Fig. 2,D) treatments resulted in a somewhat slower accumulation of ^{14}C-residues in the blood but the maximum concentrations were similar to that observed with carbaryl. The organophosphorus residues did not dissipate after reaching peak concentrations as did those of carbaryl and chlordane. Rapid ester hydrolysis of carbaryl, leptophos and parathion was evidenced by the different levels of radiocarbon in the blood following treatment with the same chemical, but with the radioactive carbon on the acid or alcohol moieties. In each case, the levels of residues in the blood were almost doubled when the radiolabel was on the alcohol portion of the molecule.

Levels of ^{14}C-residues in selected tissues of the rats one hour after treatment are given in Table 1. Concentrations in the lungs were highest with leptophos and chlordane, 30 and 24%

FIGURE 2.



^{14}C-Insecticide equivalents in the blood of rats following inhalation of the indicated radioactive preparation.

TABLE 1.

Residues in tissues of rats 1 hour after inhalation of ^{14}C-insecticides.

	% of administered radiocarbon/tissue			
Insecticide	Liver	Lung	Kidney	Bladder[a]
Carbaryl-ring-^{14}C	4.8	10.5	3.7	5.9
Carbaryl-carbonyl-^{14}C	9.2	9.2	2.9	2.7
Leptophos-phenoxy-^{14}C	8.9	31.8	3.9	4.8
Leptophos-phenyl-^{14}C	15.3	29.4	3.3	2.3
Parathion-ring-^{14}C	4.0	8.1	10.7	18.0
Parathion-ethyl-^{14}C	8.5	7.3	2.5	10.9
Chlordane	19.6	23.9	.3	.1

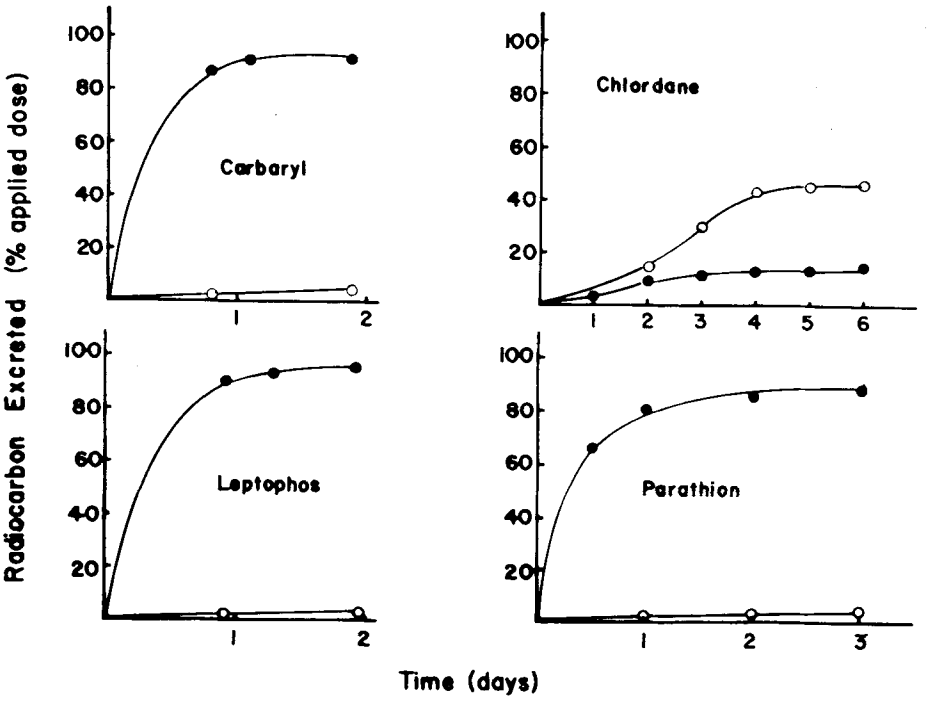
[a] Includes urine contained therein.

of the inhaled dose, while carbaryl and parathion residues were only one-third these levels. Results obtained with those compounds radiolabeled on the acid and alcohol moieties were very similar, indicating that the ester linkages were intact.

With carbaryl, parathion, and leptophos, residues in the kidney and bladder at the end of 60 minutes were higher for the ^{14}C-alcohol-labeled insecticide than for the corresponding ^{14}C-acid-labeled compound. The liver, on the other hand, contained higher residues with the ^{14}C-acid-labeled materials, demonstrating that the acid moieties released upon hydrolysis were not removed from the liver as rapidly as the alcohol moieties. That carbaryl showed higher ^{14}C-equivalents in the liver suggests that there was a delay between the formation of methyl carbamic acid and its further degradation to carbon dioxide. Chlordane-^{14}C residues in the liver were equivalent to 20% of the dose but only trace levels were detected in the kidney or bladder (Table 1).

While there was rapid absorption of the inhaled compounds into the body following exhalation, the excretion rates also were quite rapid (Fig. 3). Carbaryl, leptophos, and parathion

FIGURE 3.



Excretion of radiocarbon following inhalation of ^{14}C-ring-insecticides. • Urine; o Feces.

equivalents were eliminated in the urine in amounts greater than 90% of the inhaled doses by 3 days. The feces contained an additional 2 to 5% of the doses. For chlordane, excretion was primarily via the feces and was slower than the other compounds. About 52% of the dose was eliminated in the feces after 6 days, while the urine contained an additional 12%. The rates of excretion following inhalation are in good agreement with those reported for orally administered carbaryl (KNAAK et al. 1965), chlordane (BARNETT and DOROUGH 1974), parathion (NAKATSUGAWA et al. 1969), and leptophos (HOLMSTEAD et al. 1973). It would appear, therefore, that the ultimate fate of these insecticides when inhaled is not appreciably different than when the compounds enter the body by ingestion.

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