Acute Toxicity of o,p'-DDT to Mice

by

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Technical-grade DDT used as an insecticide contains approximately 80-90% p,p'-DDT (1,1,1-trichloro-2,2-bis-((p-chlorophenyl)) ethane), 10-20% o,p'-DDT (1,1,1-trichloro-2-((o-chlorophenyl))-2-((p-chlorophenyl))ethane) and traces of other compounds (HALLER et al. 1945). Recently, the o,p'-DDT isomer has received considerable attention because of the possibility that its estrogen-like action may disrupt reproduction in birds and mammals (reviewed by CONNEY and BURNS 1972).

It is estimated that 200 million pounds of o,p'-DDT have been released into the biosphere (BITMAN et al. 1968). Despite o,p'-DDT's abundance and the large number of publications dealing with the isomer, little information is available as to its acute toxicity to mammals.

Mixtures of pesticides are known to interact synergistically and/or antagonistically to alter each other's toxicity (ZAVON 1969). Thus, we measured separately the acute toxicities of pure o,p' and p,p' DDT isomers and a mixture (technical-DDT) to determine whether the toxicity of technical-DDT results primarily from one component or from interactions between components.

METHODS

Chemicals: o,p'-DDT was purchased from Aldrich Chemical Co. (Lot #110407, shown to contain 1.059% p,p'-DDT by BITMAN et al. 1971); p,p'-DDT (Aldrich) was 99+% pure. Technical-grade DDT (Eastman Organic Chemicals) was analyzed by gas-liquid chromatography and found to contain 79% p,p'-DDT, 20% o,p'-DDT and less than 1% other compounds.

Animals and Treatments:

A) Comparative Toxicities of o,p'-DDT, p,p'-DDT and Technical-DDT

Female C3H mice (Cumberland View Farms, Clinton, Tennessee), age 16-18 months, were assigned to treatment groups by use of a random number table. For each substance tested (o,p'-DDT, p,p'-DDT, technical-DDT) 5 doses with 20 mice/dose were used. Doses were chosen through preliminary tests and were 200-800 mg/kg body weight for p,p' and technical-DDT; the dose range for o,p'-DDT was 1200-3600 mg/kg.

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Toxicants were given as a single intraperitoneal injection in a constant volume (0.3 cc) of corn oil. After injection, animals were kept in a quiet room at 74° F and the time of death was recorded for individual mice. Food and water were available ad libitum both before and after injections. LD_{50} values 7 days after injection were calculated by weighted probit analysis (FISHER and YATES 1957).

B) Sex Difference in Toxicity of DDT Isomers

Additional groups of both castrated and intact male C3H mice were treated as above. Calculated LD_{50} values were compared with those observed in female C3H mice at 3-days after injection. 7-day LD_{50} values could not be used in this comparison because mortality at 7 days was 100% for intact male mice at the 3 highest doses of p,p' and technical-DDT.

C) Mortality in Mice Fed DDT Isomers

DDT was added to the diet by blending ethanolic solutions of the isomers with Purina Laboratory Chow in a batch mixer until the ethanol had evaporated (CLEMENT and OKEY 1972). Toxicity is expressed as the time from the start of the diets until death of half the animals in the treatment group.

RESULTS AND DISCUSSION

A) Comparative Toxicities of o,p'-DDT, p,p'-DDT and Technical-DDT

It is clear from the data in TABLE 1 that the acute toxicity of technical-DDT is due almost exclusively to the p,p'-DDT isomer. Toxicity of technical-DDT is reduced in proportion to the amount of o,p'-DDT it contains; a similar relationship has been seen in salmon fed p,p' or technical-DDT (BUHLER et al. 1969). The toxicities of technical-DDT and p,p'-DDT are in the range of values reported previously for similar routes of administration to mice (OZBURN and MORRISON 1962; LEWIN, et al. 1972). The only previous report we have located for o,p'-DDT toxicity is that of DOMENJOZ (1946) who found p,p'-DDT to be approximately 8 times more toxic than o,p'-DDT when given orally in olive oil.

TABLE 1

7-day LD_{50} of DDT Isomers Injected Intraperitoneally into Female C3H Mice

Substance Tested	LD_{50} (mg/kg body weight)	95% Confidence Limits (mg/kg)
Technical-DDT	437	427-447
p,p'-DDT	333	307-359
o,p'-DDT	2369	2278-2460

B) Sex Differences in Toxicity of DDT Isomers

Intact male C3H mice were more susceptible to toxicity of all isomers than were castrated males or females (TABLE 2). BARKER and MORRISON (1966) have shown that DDT tolerance in mice is relative to body fat content; this may explain the lower susceptibility of female and castrated male mice.

Only half of the animals dying from o,p'-DDT injections exhibited the symptoms typical of poisoning by p,p'-DDT (hyperexcitability, tremors, convulsions). Previous reports that o,p'-DDT is converted metabolically to p,p'-DDT in mammals appear to be erroneous (BITMAN et al. 1971; CRANMER 1972). Thus, o,p'-DDT must exert its toxicity by means other than conversion into the more potent p,p' isomer.

TABLE 2

Sex Differences in Toxicity of DDT Isomers to C3H Mice

Substance Tested	LD_{50} (mg/kg body weight):		
	C3H Female	C3H Male (castrated)	C3H Male (intact)
Technical-DDT	580	571	461
p,p'-DDT	505	501	409
o,p'-DDT	2617	2469	1577

C) Mortality in Mice Fed DDT Isomers

o,p'-DDT is tolerated in very high doses over prolonged periods (TABLE 3). Castrated male C3H mice survived much longer than did female C3H mice fed the same dose of p,p' or technical-DDT. The greater tolerance of castrated males may again be related to body fat content, but estrogens have been shown to reduce the activity of some drug-metabolizing enzymes (CONNEY 1967).

TABLE 3

Mortality in Mice Fed DDT Isomers

Substance and Dose (ppm in diet)	LT_{50}* (days)	
	C3H Female	C3H Male (castrated)
Technical-DDT, 500 ppm	11	63
p,p'-DDT, 500 ppm	6	40
o,p'-DDT, 500 ppm	no deaths in 250 days feeding to 30 mice	no deaths in 125 days feeding to 10 mice

* time from start of diet until death of 50% of animals in the group.

We have shown here that the acute toxicity of o,p'-DDT to mice is low. It also appears that the hormonal effects of o,p'-DDT occur only at very high doses to mammals (CLEMENT and OKEY 1972). Despite its abundant release into the biosphere, o,p'-DDT is found in low concentrations in mammals (BAETCKE et al. 1972), probably because of rapid metabolism to hydroxy and methoxy products (FEIL et al. 1971). These properties would seem to indicate a possible "safe" and non-accumulative replacement for p,p'-DDT as an insecticide. Unfortunately, the toxicity of o,p'-DDT to insects tested thus far is very low (METCALF and FUKUTO 1968).

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