The Effects of Dicofol on Induction of Hepatic Microsomal Metabolism in Rats

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In a comparative study, the induction effects of dicofol, technical Kethane, and DDT on hepatic microsomal and cytosolic enzyme activities in rats were compared with those effects produced by phenobarbital (PB) and β-naphthoflavone (BNF). Male rats (ca. 220 g) were injected ip for 4 consecutive days with 1.0 ml of vehicle containing either dicofol (3.5, 15.0, 29.5, or 59.0 mM), Kethane (dicofol content equal to 29.5 or 59.0 mM), DDT (59.0 mM), or BNF (36.7 mM). Liver weights, microsomal protein, and cytochrome P-450 concentrations and microsomal and cytosolic enzyme specific activities were measured. Dicofol produced dose-related increases in all of the parameters measured except liver weight and cytosolic epoxide hydrolase activity. At a concentration of 59.0 mM, dicofol increased the concentrations of microsomal protein (1.7-fold) and cytochrome P-450 (1.9-fold), and the specific activities of cytochrome c reductase (1.6-fold), ethoxy- coumaric O-deethylase (2.3-fold), nitroreductase (3.6-fold), microsomal epoxide hydrolase (2.6-fold), and glutathione S-transferase (2.9-fold). The induction potencies of dicofol was equivalent to Kethane, DDT, and PB at equimolar (59.0 mM) concentrations of each.

INTRODUCTION

Dicofol, the active component of Kethane azaricide, is one of the few organochlorine pesticides that still receives widespread agricultural application. An estimated 2.0 to 2.5 million pounds of dicofol active ingredient is applied annually in the United States, primarily for mite control by the cotton and citrus industries in California, Florida, Texas, and Arizona (1).

Recent concerns about the continued agricultural use of Kethane are that contaminants including DDT, DDD, DDE, and their isomers and analogs, collectively termed DDEs, pose a significant threat to populations of endangered species of birds as a result of effects on eggshell thinning (2). More recently, however, dicofol itself has been shown to produce significant eggshell thinning in birds (3).

Several theories have been formulated to account for the adverse effects of organochlorines on avian reproduction: (1) the induction of hepatic mixed-function oxygenase (MFO) enzymes resulting in increased metabolism of endogenous steroids and subsequent alterations in endocrine status (4), (2) the inhibition of calcium-ATPase in the shell-forming gland (5), and (3) an estrogenic action resulting in thyroid hormone imbalance (6). While DDT induction of MFO has not been correlated with eggshell thinning, it has been shown (4) to effect endocrine imbalances in pigeons, resulting in disturbances in courtship behavior and nesting cycles. Alternatively, the DDT metabolite, DDE, strongly inhibits calcium-ATPase in the shell-forming gland of Pekin ducks (5). As there is no firm evidence for the metabolic conversion of dicofol to DDE (7–9), an induction phenomenon or an estrogenic effect may play a more significant role in the adverse effects of DDT analogs on shell formation than was believed previously.

While the effects of DDT on induction of hepatic drug metabolizing activity have been well characterized (10–19), those of dicofol have received only minor investiga-
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tion (10, 12–14). Currently, no data are available on the hepatic induction effects of dicofol and Kelthane in the following areas: (1) the specific type (i.e., phenobarbital type or 3-methylcholanthrene type) of induction response elicited, (2) the relative potency of dicofol as an inducer in the isomeric combination that exists in technical Kelthane (i.e., 16% o,p'-dicofol and 69% p,p'-dicofol), and (3) the contribution of contaminants of technical Kelthane (20), including DDT, to the induction effects of dicofol. The present research was conducted with the intention of filling these data gaps.

MATERIALS AND METHODS

Experimental design. Characterization of the type of induction response elicited by dicofol and Kelthane was performed by measuring the effects of each on rat hepatic morphology (i.e., gross liver weights and the concentrations of microsomal protein and cytochrome P-450) and the specific activities of cytochrome c reductase, amino-pyrine N-deethylase (APNID), ethoxy-coumarin O-deethylase (ECOD), microsomal epoxide hydrolase (mEH), cytosolic epoxide hydrolase (cEH), and glutathione S-transferase (GST), and comparing the pattern of induction responses to those elicited by phenobarbital (PhB) and p-naphthoflavone (BNF).

The relative potencies of dicofol, Kelthane, and DDT as inducers were determined by comparing the effects of equivalent doses (59.0 mM) of each on the indices of induction described in those effects elicited by an equivalent dose of PhB, selected as 60 mg/kg/day (i.e., 59.0 mM). Dicofol and DDT treatments contained the o,p' and p,p' isomers of each in proportions of 18.6 and 81.4%, respectively; analysis showed that these were the isomeric proportions in which dicofol exists in Kelthane.

The contribution of DDT contaminants in Kelthane to the induction effects of dicofol was determined by comparing the induction responses elicited by equimolar (59.0 mM) doses of dicofol and Kelthane (dicofol content 59.0 mM). Chemicals. Kelthane (15.8% o,p'-dicofol, 69.2% p,p'-dicofol, and 15.0% impurities including DDT) and the o,p' and p,p' isomers of dicofol (98.8%) were supplied by Rohm & Haas Co. (Spring house, PA). The o,p' and p,p' isomers of DDT (99.0%), β-naphthoflavone (98.0%), and amino-pyrene were purchased from Aldrich Chemical Co. (Milwaukee, WI). Sodium phenobarbital was obtained from J. T. Baker Chemical Co. (Phillipsburg, N.J.). Ethoxy-coumarin was purchased from Sigma Chemical Co. (St. Louis, MO). [3H]cys and [3H]trans-stilbene oxide were prepared by Dr. Bruce Himmel of as described previously (21).

Animals and treatments. Adult male rats (Sprague–Dawley, ca. 250 g, Bantin & Kingman, Inc.) were assigned randomly to one control and nine treatment groups, six animals per group, as indicated in Table 1. Feed and water were available ad libitum.

Treatment consisted of daily intraperitoneal (ip) injections of 1.0 ml of dose solution for 4 consecutive days. Except for sodium PhB, which was administered in sterilized saline (0.9%), all chemicals were administered in sterilized peanut oil as the vehicle. Control animals received sterilized peanut oil alone.

Preparation of microsomes. Twenty-four hours after the last treatment, the animals were terminated by cervical dislocation. Liver were immediately removed, rinsed in 150 mM KCl, blotted dry, and weighed. Microsomes were prepared as described previously (22). Approximately 10 g portions of liver were homogenized in 2 vol of
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Liver weight* (g)</th>
<th>Microsomal protein concentration (mg protein/liver)</th>
<th>Cytochrome P-450 concentration (nmol/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>13.41 ± 0.88</td>
<td>15.75 ± 1.61</td>
<td>0.10 ± 0.04</td>
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<tr>
<td>Phenytoin</td>
<td>40.0</td>
<td>59.0</td>
<td>15.72 ± 0.53</td>
<td>24.00 ± 0.981</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(119)</td>
<td>(158)</td>
</tr>
<tr>
<td>Kethamine</td>
<td>40.0</td>
<td>36.7</td>
<td>15.15 ± 1.00</td>
<td>14.41 ± 0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(115)</td>
<td>(120)</td>
</tr>
<tr>
<td></td>
<td>51.4</td>
<td>29.0***</td>
<td>14.40 ± 0.79†</td>
<td>26.15 ± 1.78†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(106)</td>
<td>(171)</td>
</tr>
<tr>
<td></td>
<td>102.9</td>
<td>59.0***</td>
<td>16.67 ± 0.72†</td>
<td>27.36 ± 1.51†</td>
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<tr>
<td></td>
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<td></td>
<td>(122)</td>
<td>(179)</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>1.5</td>
<td>12.62 ± 0.53†</td>
<td>19.99 ± 1.34†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(96)</td>
<td>(131)</td>
</tr>
<tr>
<td></td>
<td>21.9</td>
<td>15.0</td>
<td>14.51 ± 0.79†</td>
<td>21.75 ± 2.024†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(118)</td>
<td>(139)</td>
</tr>
<tr>
<td></td>
<td>43.7</td>
<td>29.5</td>
<td>15.00 ± 0.40†</td>
<td>25.78 ± 1.067†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(113)</td>
<td>(168)</td>
</tr>
<tr>
<td></td>
<td>87.4</td>
<td>59.0</td>
<td>14.84 ± 0.36†</td>
<td>25.65 ± 1.315†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(113)</td>
<td>(168)</td>
</tr>
<tr>
<td></td>
<td>83.7</td>
<td>59.0</td>
<td>14.43 ± 0.74†</td>
<td>24.48 ± 0.871†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(106)</td>
<td>(145)</td>
</tr>
</tbody>
</table>

* Data ± SEM followed by the same letter in a column are not significantly different from one another (P < 0.05) by Duncan's new multiple range test.

** Mean percentage of control value.

*** Concentration of dicofol component.

† Mean of the treatment group is significantly different (P < 0.05) from that of the control group (Dunnett's t'

 Test).

Cytochrome P-450.

ice-cold homogenization buffer (20 mM Tris–HCl, 1.15% KCl, pH 7.4) and centrifuged at 16,800g for 28 min at 0–4°C. The supernatant was centrifuged at 105,000g for 75 min, and the cytosolic fraction was frozen at −80°C for cytosome enzyme measurements. The microsomal pellet was re-suspended in 15 mL of wash buffer (0.4 M sucrose, 77 mM sodium pyrophosphate, pH 7.5) and centrifuged as above. The final microsomal pellet was re-suspended in a volume of 150 mM KCl to yield ca. 30 mg protein/mL. Microsomal protein concentrations were determined colorimetrically by the biuret method using a BSA standard (23).

Cytochrome P-450 concentrations were measured spectrophotometrically by the carbon monoxide difference spectral method of Omura and Sato (24) in microsomes diluted with 100 mM Tris buffer (pH 7.4) to 1.0 mg/mL.

Enzyme activities. NADPH cytochrome c reductase activity was measured spectrophotometrically by the method of Pederson et al. (25) using concentrations of 0.1 mg/mL protein, 0.26 mM cytochrome c, and 2.58 mM NADPH. Specific activities of APND and ECOX were measured by standard colorimetric (41) and fluorometric (42) assays, respectively, using substrate concentrations of 40 mM aminopyrine and 0.83 mM erythroxylamine. Both APND and ECOX assays were performed using microsomal protein concentrations of 0.8 mg/mL and an incubation time of 20 min.
The activities of mEH, eEH, and GST were assayed by a single-step radiometric
nutrition method modified from Hill et al. (21). For mEH and GST, microsomal pro-
tein was incubated with [14C]-cis-stilbene oxide (5 x 10^{-3} M) or cytochrome
protein with [3H]-cis-stilbene oxide (5 x 10^{-6} M) plus glutathione (5 mM), respectively, for
10 min at 37°C. For eEH, cytoxal was preincubated with 0.5 mM diethylmaleate
for 10 min at room temperature to deplete endogenous glutathione (26), and then in-
cubated with [14C]-stilbene oxide (5 x 10^{-3} M) for 10 min at 37°C. The reactions
were terminated by extraction of the epoxide mEH, eEH, or epoxide and did
(GST), with isooctane or hexane, respec-
tively. Reaction products were quantitated by liquid scintillation counting of an aliquot
(50 µl) of the aqueous phase.

Statistical analysis. Means and standard errors were calculated for all measure-
ments n control (n = 5) and treatment (n = 5) groups. Data for each measurement
were subjected to one-way analysis of vari-
ance and Bartlett’s test for heterogeneity
of variance. The significance of the differ-
ences between treatment and control
means for each measurement was deter-
mined using Dunnett’s t test. Comparisons
between equimolar treatments were made using Bonferroni’s test. Individual com-
parsions among different dose groups
within a specific treatment were made
using Duncan’s new multiple range test.

RESULTS

Effects on liver morphological indices.
There were no significant (P < 0.05) effects of any of the administered chemicals on the
liver weights of treated rats relative to con-
trols (Table 1). Animals receiving the three
higher doses of diocofol had significantly (P
< 0.05) greater mean liver weights than
those of the low-dose diocofol group. How-
ever, this apparent dose-related effect of
diocofol treatment on liver weights most
likely represents an artifact, as the mean
liver weight of the low-dose diocofol group
was lower than that of the control group.

In all treatment groups, other than the
ones receiving BNF or the lowest dose of
diocofol, mean microsomal protein con-
centrations were significantly (P < 0.05) in-
creased relative to that in the control group
(Table 1). The microsomal protein concen-
tration in animals treated with the highest
dose of Ketamine (1.79 times control) was
significantly (P < 0.50) greater than the
concentration measured in animals treated
with an equimolar (59.0 mM) dose of DDT
(1.45 times control) but was not signifi-
cantly greater than that produced by equi-
molar doses of PhB (1.38 times control) or
diocofol (1.66 times control). Increasing
doses of diocofol up to 43.7 mg/kg produced
the corresponding increases in mean micro-
somal protein concentrations.

Cytochrome P-450 concentrations were
significantly (P < 0.05) increased in all
treatment groups except for those receiving
BNF or the lowest dose of diocofol. For an-
imals treated with diocofol or Ketamine the
reduced CO spectrum exhibited maximal
absorbance at 450 nm. In animals treated
with BNF, there was a significant shift of
the reduced CO spectral maximum from an
average of 450 to 448 nm. Diocofol-treated
groups exhibited a dose-response trend, with
increasing doses of diocofol producing cor-
respondingly increased cytochrome
P-450 concentrations.

Effects on liver microsomal enzyme ac-
tivities. The PhB, high-dose Ketamine, and
high-dose diocofol treatments resulted in
significantly (P < 0.05) increased mean cy-
tochrome P reductase activities, with
values 1.5, 1.7, and 1.6 times that of the
control, respectively (Table 2). For all other
groups, the cytochrome P reductase activi-
ties were not significantly (P > 0.05) greater
than that of the control.

Mean ECOD activities were significantly
(P < 0.05) increased for all of the chemical
treatment groups except the low-dose di-
cofol group. However, the response to
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean specific activity (nembutal mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cytochrome c/indoline</td>
</tr>
<tr>
<td></td>
<td>Ethoxyresorcinol/</td>
</tr>
<tr>
<td></td>
<td>Acetylcholinase/</td>
</tr>
<tr>
<td></td>
<td>Antipsychine/</td>
</tr>
<tr>
<td></td>
<td>Microsomal apoalbuminogenesis</td>
</tr>
<tr>
<td>Control</td>
<td>—</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>60.0 59.0</td>
</tr>
<tr>
<td>Phenothiazine</td>
<td>40.0 36.7</td>
</tr>
<tr>
<td>Kelthane</td>
<td>51.4 29.0***</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephaline</td>
<td>102.9 59.0***</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Diocel</td>
<td>2.2 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Desy</td>
<td>87.4 59.0</td>
</tr>
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<tr>
<td>Desy</td>
<td>87.4 59.0</td>
</tr>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SEM followed by the same letter in a column are not significantly different from the means of other dose groups within the given treatment according to Duncan's multiple range test (P < 0.05).

** Mean percentage of control value.

*** Mean percentage of control weight.

1 Mean of the treatment group is significantly different (P < 0.05) from that of the control group (Demmett's test).

BNF (ca. 12.4 times control) was much greater in magnitude than was the next highest response, that to Phl (2.4 times control). Mean APND activities were significantly (P < 0.05) increased in all treatment groups except for the group receiving BNF, the activity produced by the high-dose diocel treatment (3.0 times control) was significantly (P < 0.05) greater than that produced by an equimolar (59.0 mM) dose of Phl (0.06 times control), but was not significantly greater than that produced by equimolar doses of Kelthane (ca. 2.5 times control) or DDT (ca. 2.2 times control).

Mean MHE activities were significantly (P < 0.05) increased in all treatment groups except in those which received BNF and the lowest doses of diocel. Differences between the mHE activities produced in response to equimolar (59.0 mM) doses of Phl, Kelthane, diocel, and DDT were not significantly different.

For all of the microsomal enzyme activities measured, there were dose–response–related trends in the response to diocel treatment, with increasing doses of diocel producing corresponding increases in the mean enzyme activities measured (Table 2).
### Table 3
Effects of Chemical Treatments on Rat Liver Cytosolic Enzyme Specific Activities

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Mean specific activity (units/mg protein)</th>
<th>Cytosolic epoxide hydrolase</th>
<th>Glutathione S-transferase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/kg</td>
<td>mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>—</td>
<td>—</td>
<td>0.089 ± 0.015 (100)</td>
<td>7.76 ± 0.23 (100)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>60.0</td>
<td>59.0</td>
<td>0.078 ± 0.016 (70)</td>
<td>16.81 ± 1.45 (219)</td>
</tr>
<tr>
<td>β-Naphthoflavone</td>
<td>40.0</td>
<td>36.7</td>
<td>0.103 ± 0.017 (134)</td>
<td>13.66 ± 1.33 (170)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>51.4</td>
<td>29.5***</td>
<td>0.092 ± 0.018 (113)</td>
<td>16.28 ± 1.64 (219)</td>
</tr>
<tr>
<td></td>
<td>102.9</td>
<td>59.0</td>
<td>0.079 ± 0.016 (85)</td>
<td>23.40 ± 2.23 (302)</td>
</tr>
<tr>
<td>Dicofol</td>
<td>2.2</td>
<td>1.5</td>
<td>0.086 ± 0.009 (108)</td>
<td>11.96 ± 2.36 (152)</td>
</tr>
<tr>
<td></td>
<td>21.9</td>
<td>15.0</td>
<td>0.097 ± 0.014 (78)</td>
<td>14.96 ± 3.62 (191)</td>
</tr>
<tr>
<td></td>
<td>43.7</td>
<td>29.5</td>
<td>0.068 ± 0.009 (83)</td>
<td>14.61 ± 2.63 (187)</td>
</tr>
<tr>
<td></td>
<td>87.4</td>
<td>59.0</td>
<td>0.086 ± 0.015 (116)</td>
<td>12.50 ± 1.98 (280)</td>
</tr>
<tr>
<td>DDT</td>
<td>83.7</td>
<td>59.0</td>
<td>0.086 ± 0.013 (90)</td>
<td>16.37 ± 1.51 (212)</td>
</tr>
</tbody>
</table>

* Means ± SEM followed by the same letter in a column are not significantly different from the means of other dose groups within a given treatment according to Duncan's multiple range test (P < 0.05).

** Mean percentage of control value.

*** Concentration of dicofol component.

† Mean of the treatment group is significantly different (P < 0.05) from that of the control group (Dunnnett's test).

**Discussion**

In this study, dicofol and its technical formulation, Ketamine, produced significant increases in microsomal protein and cytochrome P-450 concentrations, the coupled reductase (cytochrome c reductase), several cytochrome P-450-dependent monoxygenase (cytochrome P-450 monoxygenase) activities (APND and mEH) and GST activity. These observations are consistent with PhB-type induction, and are in agreement with previous reports (11, 13, 15–19) demonstrating the induction effects of dicofol and Ketamine on SER proliferation, liver weight, and cytochrome P-450 monoxygenase activities, including aldrin epoxidase, heptachlor epoxidase, APND, aniline hydroxylase, and hexobarbital oxidase. By contrast, BNF, a 3-MC-type inducer (17), produced no significant changes in any of these parameters, except for the activity of GST, which is consistent with published data (28). In addition, BNF induced the cytochrome P-448 hemoprotein and produced a marked (ca. 13-fold) increase in the activity of ECO, both indices of 3-MC-type induction (29, 30). From the pattern of induction responses observed, it can be concluded that dicofol and Ketamine are inducers of hepatic MFO of the PhB type.

There were no significant differences between the effects of dicofol and Ketamine, containing equimolar doses of dicofol, on any of the indices of induction that were
measured (Tables 1–3). Thus, the non-dioic components of Ketthane, including DDT which are also inducers of hepatic MFOs (13, 16, 17), do not contribute significantly to the induction potency of dioicof.

The threshold for dioicof’s effects on hepatic induction in rats was demonstrated to be between 2.2 and ca. 22 mg/kg (16) under the exposure regime used in this study. Also demonstrated was the significant potency of dioicof on hepatic induction. On most indices of liver induction that were measured, dioicof was equipotent with Phb and DDT (Tables 1–3). In previous studies (16, 17, 19), dioicof has been shown to approach p,p’-DDT in potency on the induction of cytochrome P-450 monoxygenase activities in rats and mice. Alternatively et al. (17) demonstrated that dioicof, specific isomer not mentioned, was less potent an inducer of mouse liver aniline hydroxylase activity than were the p,p’- and m,p’- isomers of DDT but was more potent than the o,o’ isomer.

In the present study, animals were treated with a mixture of isomers of dioicof (81.4% p,p’- isomer and 18.6% a,p’ isomers) the same proportions present in the technical formulation Ketthane. When dioicof in this isomeric composition was compared with DDT (of identical isomer composition) with respect to its effects on hepatic induction, no significant differences in potencies were observed. In mice, p,p’-DDT is ca. five times more potent an inducer of hepatic cytochrome P-450 monoxygenase activity than is a,p’-DDT (17). Thus, a mixture of the two isomers would be expected to exhibit less induction potency than the p,p’- isomer, alone. It is quite possible that with a wide variation in the potencies of the p,p’ and o,p’ isomers is not manifested in the case of dioicof and that the induction potency of the mixture of isomers does not significantly differ from either isomer alone. Alternatively, there may be species variation between rats and mice with respect to the selectivity of induction effects by different isomers of chlorinated hydrocarbons. Molecular characteristics conferring high enzyme-inducing potency to structurally analogous of DDT include a high degree of electron withdrawal from the bridge carbon by electronegative groups (16). Dioicof, containing a hydroxylated bridge carbon, may actually have greater potential as an MFO inducer than does DDT, based on structural considerations. However, a higher rate of metabolism to less active metabolites such as 4,4-dichlorobenzhydrol (16) may be the reason that its actual induction potency is no greater than that of DDT.

This study has confirmed that dioicof and its technical formulation are Phb-type inducers of hepatic cytochrome P-450 monoxygenase activity of equal potency to DDT (of the same isomer composition). The microsomal cytochrome P-450 monoxygenase system is responsible for the metabolism of a wide variety of xenogenous and endogenous lipophilic compounds including steroids essential for normal reproductive function (28). Induction of cytochrome P-450 monoxygenases by compounds such as Phb and chlorinated hydrocarbon (e.g., DDT, DDE, and dieldrin) has resulted in accelerated metabolism of steroid hormones in vitro (4, 31, 32), and has been correlated with increased metabolism and modified action of exogenously administered steroids including progesterone, testosterone, and estradiol in vivo (33–37). Alterations in avian reproduction (e.g., suppressed courtship behavior, delayed breeding cycles, or failure to lay eggs entirely) in birds exposed to DDT, PCBs, or dieldrin are believed to be associated with decreases in plasma estrogen levels resulting from the induction of cytochrome P-450 monoxygenases (4, 38, 39). These effects on reproduction may be just as important in the population declines of some species of predatory birds as is eggshell thinning (40).

It recently has been demonstrated (3) in
the ring dove that exposure to dicofol resu-
results in significant eggshell thinning. A com-
bination of altered reproductive be-
vhavior produced by the induction of cy-
tochrom P-450 monoxygenases and re-
sultant changes in hormonal status, and di-
frect eggshell thinning effects of dicofol, could have drastic effects on raptor popula-
tions in the wild. In light of these concerns, these authors intend to extend their study of the induction potential of dicofol to in-
clude its effects on avians.

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