Dose-dependent Extent Microsomal Enzyme Induction by Aldrin and Dieldrin in Rats

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Numerous investigations during past several years have demonstrated that organochlorine pesticides have the ability to induce synthesis of hepatic microsomal enzymes. However, only some of these studies have been done with regard to the levels of pesticides that are encountered in the environment /Kinoshita et al. 1966, Street et al. 1966, Gillett et al. 1968/.

In light of these investigations it was interesting to study the relationship between doses of inducing agents and the rate and extent of enzyme induction. Observations described previously /Krampl 1974/ showed that enzyme induction had reached maximum within the first two weeks of three-months oral administration with aldrin, dieldrin and heptachlor. The present investigation was undertaken to determine the extent of enzyme induction in dependence on magnitude dose of aldrin and dieldrin, cyclodiene pesticides.

Materials and Methods

Male Wistar rats, 120-150 g maintained on Larsen diet were used in these experiments and were fasted overnight prior to killing.

Experimental animals received daily 0.05, 0.25, 1.25 and 2.50 mg/kg body weight of aldrin and dieldrin /pure grade/ for a period thirteen days. Dose were administered in pure vegetable oil by means of oral tube. Control animals received only oil. Each group consisted of 6 animals.

Both experimental and control animals were sacrificed by decapitation on the fourteenth day.

Two reactions catalyzed exclusively by microsomal enzymes were included in this study.

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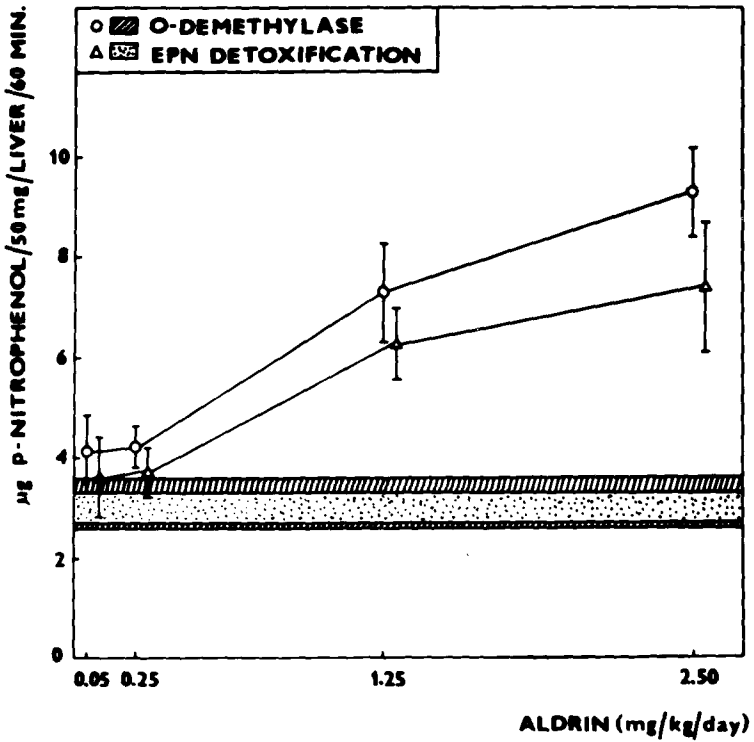

FIGURE 1. Dose-dependent extent of induction of O-demethylase activity and EPN detoxification by various oral doses of aldrin. The mean values and SD of enzyme activity at 24 hours following last administration of aldrin. Rats received aldrin for 13 days.

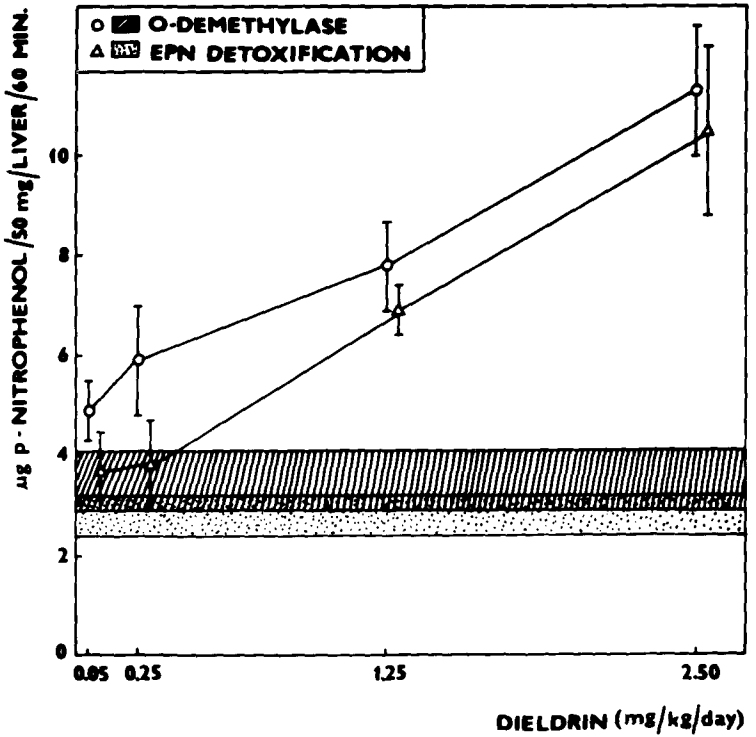

FIGURE 2. Dose-dependent extent of induction of O-demethylase activity and EPN detoxification by various oral doses of dieldrin. The mean values and SD of enzyme activity at 24 hours following last administration of dieldrin. Rats received dieldrin for 13 days.

They were the oxidative detoxification of O-ethyl O-/4-nitrophenyl/ phenylphosphonothioate /EPN/[1] and the O-demethylation of p-nitroanisole. Activity of these enzymes was determined by the method of Kinoshita et al. /1966/ and was expressed as mg of p-nitrophenol formed by 50 mg of liver in 60 minutes. Microsomal protein was assayed by the procedure of Lowry et al. /1951/.

Results and Conclusions

The extent of induction of O-demethylase activity and EPN detoxification system by various oral doses of aldrin is depicted in Figure 1. Significant differences /$P \leq 0.05 - 0.001$/ between the mean values of microsomal enzyme activity of both enzyme systems were observed at all doses with the exception of values both enzymes at 0.05 and 0.25 mg doses of aldrin.

Dieldrin was more effective than aldrin in causing induction of both microsomal enzymes /Figure 2/. Differences between the mean values of O-demethylase activity and EPN detoxification system were statistically significant /$P \leq 0.01 - 0.001$/ at all doses of dieldrin except EPN detoxification at 0.05 and 0.25 mg doses.

These observations strongly suggest dependence of changes of microsomal enzyme activity on magnitude dose of aldrin and dieldrin.

Dose-dependent increases in relative liver weight and microsomal protein also occured with doses of 0.05 - 2.50 mg of both pesticides /Table 1,2/ with the exception of both liver weight and microsomal protein at 1.25 mg dose of aldrin /Table 1/ and except microsomal protein concentration at 2.50 mg dose of dieldrin /Table 2/.

On the basis of these data it can be conclude that relative liver weight can in certain extent serve as a criterion in evaluation of inducing ability of aldrin and dieldrin, but only in relation to the other criterions.

It is assumed that enzyme induction represents an increased concentration of enzyme protein /Conney 1967, Street 1969/ although the validity of this mechanism by pesticides has not been confirmed.

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[1] O-ethyl O-/4-nitrophenyl/ phenylphosphonothioate /EPN/ was supplied gratis by the DuPont de Nemours and Co., Wilmington, Delaware, USA

Table 1

The mean values and SD of liver weight and microsomal protein at 24 hours following last administration of aldrin. Rats received aldrin for 13 days.

Treatment	Liver weight /g/100 g of body weight/	Microsomal protein /mg/g of liver/
Pure vegetable oil /Controls; N=6/	3.28 ± 0.22	9.5 ± 1.6
Aldrin, 0.05 mg/kg/day /N=6/	3.66 ± 0.14[a]	10.8 ± 1.5
Aldrin, 0.25 mg/kg/day /N=6/	3.74 ± 0.46	16.5 ± 1.4[ab]
Aldrin, 1.25 mg/kg/day /N=6/	3.71 ± 0.28[a]	15.7 ± 2.4[ab]
Aldrin, 2.50 mg/kg/day /N=6/	3.85 ± 0.57	19.1 ± 1.4[abcd]

[a]Significantly different from control group /$P<0.05$-0.001/

[b]Significantly different from group treated 0.05 mg aldrin /$P<0.01$ - 0.001/

[c]Significantly different from group treated 0.25 mg aldrin /$P<0.05$/

[d]Significantly different from group treated 1.25 mg aldrin /$P<0.05$/

Table 2

The mean values and SD of liver weight and microsomal protein at 24 hours following last administration of dieldrin. Rats received dieldrin for 13 days.

Treatment	Liver weight /g/100 g of body weight/	Microsomal protein /mg/g of liver/
Pure vegetable oil /Controls; N=6/	3.11 ± 0.10	9.0 ± 1.7
Dieldrin, 0.05mg/kg/day /N=6/	3.17 ± 0.14	9.5 ± 1.5
Dieldrin, 0.25mg/kg/day /N=6/	3.48 ± 0.25[ab]	15.7 ± 2.1[ab]
Dieldrin, 1.25mg/kg/day /N=6/	3.58 ± 0.27[ab]	16.4 ± 2.6[ab]
Dieldrin, 2.50mg/kg/day /N=6/	3.89 ± 0.14[abcd]	16.0 ± 0.9[ab]

[a] Significantly different from control group /$P \leq 0.05$-0.001/

[b] Significantly different from group treated 0.05 mg dieldrin /$P \leq 0.05$ - 0.001/

[c] Significantly different from group treated 0.25 mg dieldrin /$P \leq 0.05$/

[d] Significantly different from group treated 1.25 mg dieldrin /$P \leq 0.05$/

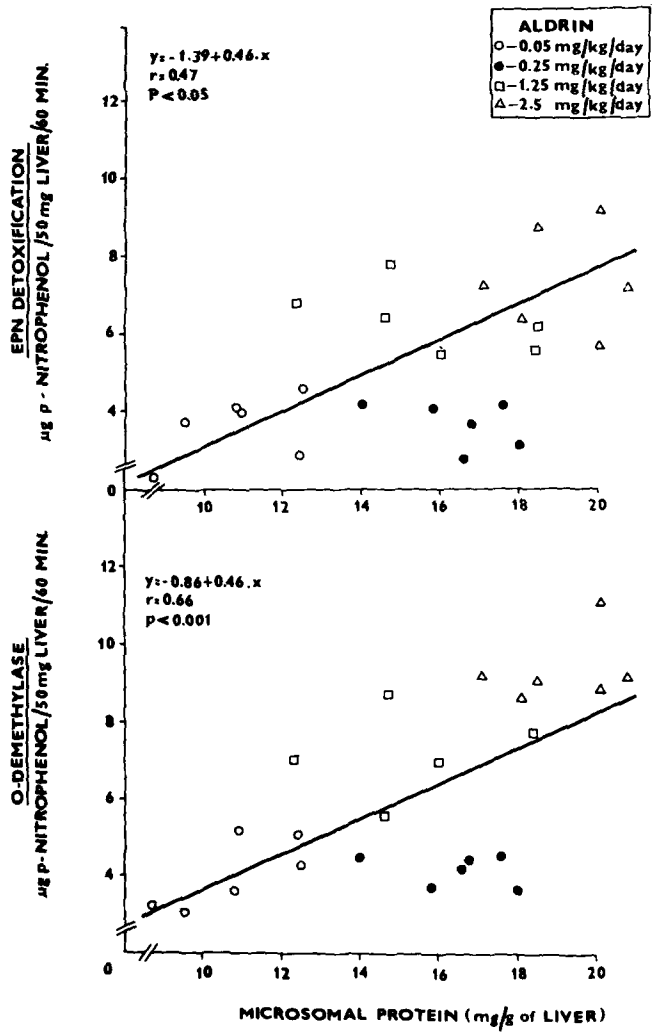

FIGURE 3. Correlations between activity of O-demethylase and EPN detoxification and microsomal protein at 24 hours following last administration of various doses of aldrin. Rats received aldrin for 13 days.

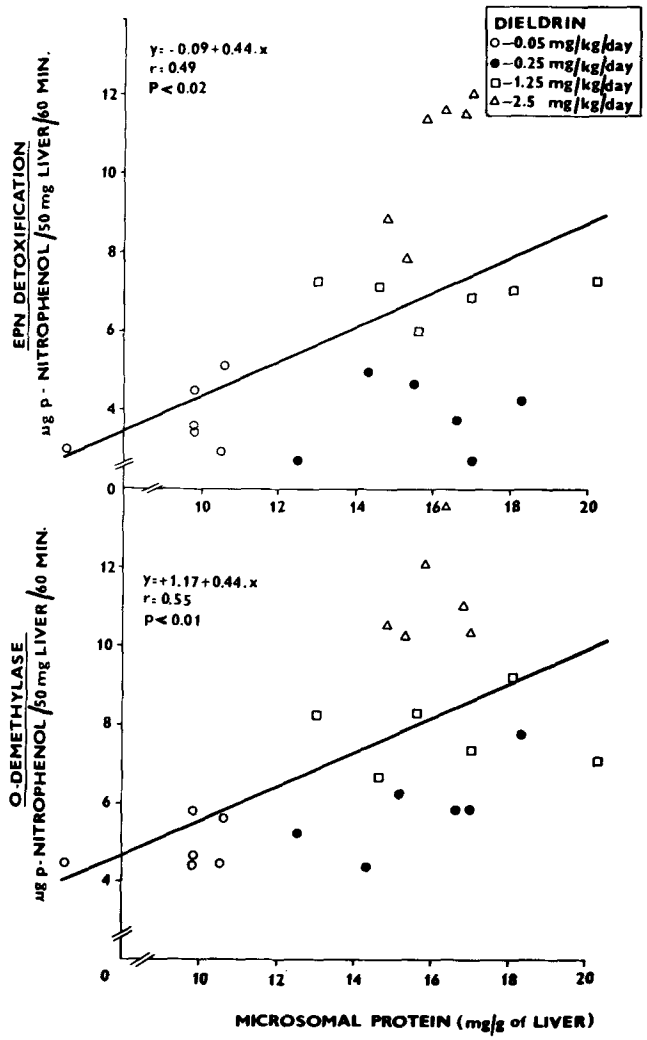

FIGURE 4. Correlations between activity of O-demethylase and EPN detoxification and microsomal protein at 24 hours following last administration of various doses of dieldrin. Rats received dieldrin for 13 days.

In the present study the increases in activity of hepatic microsomal enzymes were accompanied by increases in microsomal protein. This provided an impetus to search the quantitative relationship between the activity of O-demethylase and EPN detoxification and microsomal protein after oral administration of various doses of aldrin and dieldrin. Correlations between the increased activity of both microsomal enzyme systems and increased concentration of microsomal protein were obtained /Figures 3,4/.

This strongly suggests an actual increase in enzyme protein caused by aldrin and dieldrin. However, these results should be checked by large number of animals in several experimental groups with aldrin and dieldrin.

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