

## Endrin Excretion by the Isolated Perfused Rat Liver: A Sexual Difference<sup>1</sup> (35385)

LESLIE M. KLEVAY  
(Introduced by R. A. Kehoe)

*Department of Environmental Health, University of Cincinnati, College of Medicine,  
Cincinnati, Ohio 45219*

Chlorinated hydrocarbon insecticides are extensively used and have been found in the food chain of certain desirable animals and man. Little information is available regarding metabolism of these materials and regarding effects of chronic, low level exposures.

The toxicity of a single, oral dose of endrin as measured by the acute LD<sub>50</sub>, has been shown to be greater for females than for males in both rats (1, 2) and guinea pigs (3). More endrin is stored in the adipose tissue of female rats than in male rats (4, 5).

This study was designed to test the hypothesis that the differential toxicity and adipose tissue storage of endrin (1,2,3,4,10, 10-hexachoro-6,7-epoxy-1,4,4 $\alpha$ ,5,6,7,8,8 $\alpha$  octahydro-1,4-endo, endo-5, 8-dimethanonaphthelene<sup>2</sup>) is due to a differential hepatic excretion. The identification of the liver as the major excretory organ and the validity of the isolated, perfused rat liver technique in the study of endrin excretion has been established (6) by experiments with intact rats, and with rats with biliary fistulas and with isolated, perfused rat livers.

**Methods.** Experimental conditions have been described (6, 7). In brief, endrin-<sup>14</sup>C (sp act =  $6.58 \times 10^6$  dpm/mg) was added to the whole blood-Ringer's solution perfusate (70 ml) as an acetone solution (0.1 ml) prior to initiation of perfusion to give a concentration of 0.003 mg/ml. Radioactivity was measured in bile, after 60, 150, and 240 min of perfusion, by liquid scintillation (8).

**Results.** The results are shown in Table I, and are expressed per gram of liver, as the livers of the female rats were significantly

smaller than those of the male rats. Heterogeneity of variance (9) was demonstrated in the first collection period ( $F = 47.7$ ,  $p < 0.005$ ); the excretion of radioactivity by male livers was significantly greater than by female livers. No heterogeneity of variance was demonstrable in the subsequent periods. At 150 min the excretion by male livers was still significantly greater (9) than by female livers ( $t = 3.19$ ,  $p < 0.025$ ), but at 240 min, the difference was not significant ( $t = 2.25$ ,  $p > 0.050$ ). Previous work demonstrated that excretion by male livers approaches 100% of the dose by then (6).

No significant differences were noted between the experimental groups regarding initial period of anoxia endured by the livers or regarding the volume of bile produced. In fact, the livers of female donors endured slightly less anoxia and produced slightly more bile than did the livers of male donors.

**Discussion.** Thus the lesser toxicity of endrin and the lesser storage of endrin by male rats is explained by a greater ability of the male rat liver to excrete endrin or its metabolites. Males excreting endrin have less to store or detoxify under comparable conditions. This work confirms a more rapid excretion by intact, male rats found during 24 days of study (5).

The utility of the isolated, perfused rat liver as a rapid alternative to lengthy animal experiments in the toxicology of endrin is confirmed.

**Summary.** Isolated perfused rat liver experiments were performed using livers from male and female donors. Radiolabeled endrin added to perfusates appeared in bile of livers of male donors 2 to 12 times as rapidly as in bile of livers of female donors. These

<sup>1</sup> This investigation was supported by Public Health Service Grant No. 5 P10 ES 00159.

<sup>2</sup> Mallinckrodt Nuclear, St. Louis.

TABLE I. Cumulative Biliary Excretion of  $^{14}\text{C}$  by Isolated Perfused Rat Livers.<sup>ab</sup>

Group	(min):	(cpm/g of liver)		
		60	150	240
Males		9240 ± 1700	13,400 ± 1510	14,000 ± 1390
Females		781 ± 247	5560 ± 1960	7930 ± 2330

<sup>a</sup> Four experiments per group. The mean liver weight for the male and female groups was  $9.5 \pm 0.6$  and  $6.8 \pm 0.4$  g, respectively.

<sup>b</sup> ± Values are standard error.

findings explain the lesser toxicity and lesser adipose tissue storage of endrin in male rats, and further validate the isolated perfused liver technique as a useful method of insecticide toxicology.

1. Treon, J. F., and Cleveland, F. P., *J. Agr. Food Chem.* **3**, 402 (1955).
2. Gaines, T. B., *Toxicol. Appl. Pharmacol.* **2**, 88 (1960).
3. Treon, J. F., Cleveland, F. P., and Cappel, J., *J. Agr. Food Chem.* **3**, 842 (1955).
4. Kunze, F. M., and Laug, E. P., *Fed. Proc., Fed.*

*Amer. Soc. Exp. Biol.* **12**, 339 (1953).

5. Klein, W., Müller, W., and Korte, F., *Justus Liebigs Ann. Chem.* **713**, 180 (1968).

6. Cole, J. F., Klevay, L. M., and Zavon, M. R., *Toxicol. Appl. Pharmacol.* **16**, 547 (1970).

7. Klevay, L. M., and Hegsted, D. M., *J. Atheroscler. Res.* **8**, 329 (1968).

8. Tye, R., and Engel, J. D., *Anal. Chem.* **37**, 1225 (1965).

9. Snedecor, G. W., "Statistical Methods," 5th ed., pp. 45, 244. Iowa State Univ. Press, Ames (1956).

Received Oct. 19, 1970. P.S.E.B.M., 1971, Vol. 136.