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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Propiconazole, Male Mouse Dietary Study - Comparisons Among Pathologists - J.M. Offer, J. Hardisty and L.H. Brennecke of Hepatocellular Tumor Rates

Caswell no.323EE

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Dr. Doyle requested a comparison of 3 pathologist's (J.M. Offer, J. Hardisty and L.H. Brennnecke) observation of the number of hepatocellular tumors that occurred in the 2-year dietary study of propiconazole (CGA 64 250) in male mice.

Since only 0, 500 and 2500 ppm dose level tumors were re-evaluated by L.H. Brennecke, the statistical analysis of the comparative data from the 3 pathologists was based only on these dose levels (original study had an additional dose of 100 ppm).

(1)

Male rat survival in the propiconazole study was significantly decreased according to the trend analysis of mortality with incremental doses of propiconazole (Table 1).

Therefore tumor rate analysis was based on Peto's Prevalence tests of trends and pair-wise comparison of controls and each dose level for each set of data from each pathologist.

The comparison of combined (adenoma and/or carcinoma) hepatocellular tumor rates in terms of the statistical findings produced the same significant (significant increase in trend and significant increase in pair-wise comparison of controls and the highest dose) among all 3 pathologists. The summary of hepatocellular tumors observed in the high dose was exactly the same for all pathologists. The control data for 2 of them was the same and the other one observed one more tumor. In the 500 ppm group the number of tumors observed were 26, 25 and 23 (Table 2).

The comparison of hepatocellular carcinoma tumor rates among the 3 pathologists indicated that the statistical analysis of the data resulted in a significant increasing dose related trend in all 3 data sets. Two out of the evaluated data sets also had a significant increase in the pair-wise comparison of controls and the highest(2500 ppm) dose group. The analysis of the other observed data set resulted in a borderline significant difference in the same pair-wise comparison. The number of carcinomas observed were 26, 25 and 20 in the highest dose group among the 3 pathologists (Table 3).

The comparison of the statistical analysis of hepatocellular adenomas only also indicated the same significant results (increasing trend and pair-wise comparison of controls and the highest dose group) among the data from the 3 pathologists. There was some variation in the number of adenomas only (22, 23 and 28) observed in the highest dose group. However these differences did not differentially affect the statistical results among the pathologists (Table 4).

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Table 1. Propiconazole - Mouse Study, Male Mortality Rates+ and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53[a]	53-78	79-104[b]	Total
0	0/64	2/64	11/62	11/51	16/40	29/53(55)**
500	1/64	5/63	11/58	10/47	16/37	32/53(60)*
2500	5/64	5/59	9/54	16/45	15/29	41/55(75)*

+ Number of animals that died during interval/Number of animals alive at the beginning of the interval.

( ) percent

[a] Interim sacrifice at week 53.

[b] Final sacrifice at weeks 105.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 2. Propiconazole - Male Mouse Study, Hepatocellular Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
Tumors Combined (Adenoma &/or Carcinoma)	0	500	2500
Pathologist			
J.M. Offer (%)	28/63 (44)	25/62 (40)	48/56 (86)
p=	0.000**	0.702(n)	0.000**
J. Hardisty (%)	28/63 (44)	26/61 (43)	48/56 (86)
p=	0.000**	0.693(n)	0.000**
L.J. Brennecke (%)	27/63 (43)	23/62 (37)	48/56 (86)
p=	0.000**	0.718(n)	0.000**

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

n Negative change from control.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

Table 3. Propiconazole - Male Mouse Study, Hepatocellular Carcinoma Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
	0	500	2500
Tumors			
Carcinomas			
Pathologist			
J.M. Offer	15/62	15/60	26[a]/55
(%)	(24)	(25)	(47)
p=	0.003**	0.511	0.010*
J. Hardisty	16/62	13/60	25[b]/55
(%)	(26)	(22)	(45)
p=	0.006**	0.75(n)	0.035*
L.J. Brennecke	14/60	11/58	20[c]/54
(%)	(23)	(19)	(37)
p=	0.028*	0.801(n)	0.050

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first carcinoma.

n Negative change from control.

[a] First carcinoma observed at week 50, dose 2500 ppm.
[b] First carcinoma observed at week 50, dose 2500 ppm.
[c] First carcinoma observed at week 53, dose 2500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

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Table 4. Propiconazole - Male Mouse Study, Hepatocellular Adenoma Only Tumor Rates and Peto's Prevalence Test Results (p values)

	Dose (ppm)		
	0	500	2500
Tumors			
Adenomas Only			
J.M. Offer (%)	13/64 (20)	10[a]/62 (16)	22/56 (39)
p=	0.001**	0.668(n)	0.007**
J. Hardisty (%)	12/64 (19)	13[b]/62 (21)	23/56 (41)
p=	0.000**	0.419	0.001**
L.J. Brennecke (%)	13/64 (20)	12[c]/62 (19)	28/56 (50)
p=	0.000**	0.514(n)	0.000**

+ Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

n Negative change from control.

[a] First adenoma observed at week 44, dose 500 ppm.
[b] First adenoma observed at week 44, dose 500 ppm.
[c] First adenoma observed at week 44, dose 500 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then p<.05 and if ** then p<.01.

References

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