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Subject: Acifluorfen (Tackle): Updated Qualitative Risk Assessment. Caswell # 755D.

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This abbreviated Qualitative Risk Assessment for Acifluorfen (Tackle) updates the Lacayo memo, Quantitative Risk Assessment for Acifluorfen (Tackle/Blazer), dated Oct. 4, 1984.

Since the Blazer study was conducted at dose levels well below the MTD and the dosing regimen was changed at 16 weeks of study for the high dose, Dr. Phang requested that the updated statistical evaluation be done only on the Tackle Mice Study.

In the 18-month Tackle feeding study, a statistically significant ($p<.01$) dose related positive trend (Cochran-Armitage Test) and high dose positive comparison with control (Fisher Exact Test) was observed for male mice mortality; no survival disparities were observed in female mice, see table 1a. .

As seen in table 1b. most of the male mice mortality occurred late -- thus, there is no appropriate way to adjust for mortality by time of occurrence (ie., the Peto Prevalence Trend Test would be collapsed into one time interval for intercurrent mortality animals). However, since the bias introduced by the

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survival disparity understates the significance, the results as indicated in the next paragraph are really more significant.

For the male mice, in table 2. the Cochran-Armitage Trend Test indicates statistically significant ($p<.01$) dose related trends for liver (adenoma only, carcinoma, adenoma and/or carcinoma) and stomach (papilloma) tumors. Also, in Table 2. the Fisher Exact Test indicates statistically significant pairwise comparisons in the high dose group for each type liver tumor ($p<.01$) and stomach tumor ($p<.05$), and in the low dose group for liver adenoma only ($p<.05$) and for liver adenoma and/or carcinoma ($p<.05$).

For the female mice, in table 2. the Cochran-Armitage Trend Test indicates statistically significant dose related trends for each type liver tumor ($p<.01$) and stomach papillomas ($p<.05$). Also, in table 2. the Fisher Exact Test indicates statistically significant ($p<.01$) pairwise comparisons in the high dose for liver adenomas, and for ≥ liver adenomas and/or carinomas. Statistically significant ($p<.05$) pairwise comparisons are also seen in the high dose liver carcinomas, and stomach papillomas.

Table 1a.[+]

Mortality of Tackle Treated Animals

Dose	Male	Female
0	1**	2
625	3	2
1250	3	4
2500	10**	3

Note: Significance of trend analysis (Cochran-Armitage Trend Test) denoted at control; significance of pairwise comparison with control (Fisher Exact Test) denoted at dose level.

* $p<.05$ ** $p<.01$

Table 1b.[+]

Time Distribution of Natural Deaths

Sex	Study Time Intervals (wks)	No. of Deaths in Groups Control	625	1250	2500
Males	0-26	1[a]	0	1	1
	27-52	0	0	1	3
	53-79	0	3	1	6
Females	0-26	2[a]	0	0	1
	27-52	0	0	2	0
	53-79	0	2	2	2

[a]These deaths occurred during weeks 17-23. The deaths of two female control animals at weeks 1[illegible] and 21 are not included here because they were listed as both natural and accidental deaths.

[+]Tables 1a. & 1b. are from Carolyn Gregorio's Data Evaluation Review (Tackle: 18-month mouse oncogenicity study), pp. 5-6. Table 1a. has been modified by removing animals that died due to accidental death or cage flooding.

Table 2.

Tumor Incidence in Tackle Treated Mice[+]

	0 ppm	625 ppm	1250ppm	2500ppm
Male				
Liver				
Adenomas	8/58 (14)**	18/60 (30)*	12/56 (21)	25/59 (42)**
Carcinomas	1/48 (2)**	3/50 (6)	4/46 (9)	15/44 (34)**
Ad &/or Ca	9/58 (16)**	21/60 (35)*	16/56 (29)	40/59 (68)**
Stomach				
Papillomas	0/49 (0)**	0/46 (0)	0/43 (0)	4/40 (10)*
Female				
Liver				
Adenomas	1/55 (1)**	5/59 (5)	4/57 (4)	19/58 (19)**
Carcinomas	0/45 (0)**	1/47 (2)	1/44 (2)	5/46 (11)*
Ad &/or Ca	1/55 (2)**	6/59 (10)	5/57 (9)	24/58 (41)**
Stomach				
Papillomas	0/45 (0)*	3/48 (6)	3/44 (7)	6/45 (13)*

() Percent

[+]Tumor bearing animals/animals at risk (ie., the animals dying prior to the week of first tumor occurrence for each tumor, are removed from the animals at risk).

Note: Significance of trend analysis (Cochran-Armitage Trend Test) denoted at Control; significance of comparison with control (Fisher Exact Test) denoted at Dose level.

* $p<.05$ ** $p<.01$

These results were derived from the individual animal data compiled by Carolyn Gregorio.

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