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SUBSTANCES

Subject: Acetochlor - Qualitative Risk Assessment -
2-Year CD Rat and CD-1 Mouse Dietary Studies

Caswell no.003B

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Summmary

The qualitative risk assessment of acetochlor was based upon both the 2-year dietary study of CD-1 mice and of CD rats. The mice were fed 0, 10, 100 and 1000 ppm. and the rats 0, 18, 175 and 1750 ppm. of the compound for 78 and 104 weeks respectively. In both studies, 50 animals per sex were assigned to each dose group.

An additional 10 mice was selected for sacrifice in each sex/dose group at the end of a year. In the rat study, an additional 20 animals in each sex for doses of 0 and 1750 ppm were sacrificed at the end of a year. Also an additional 10 rats in each sex for doses of 18 and 175 ppm. of acetochlor were sacrificed at the end of a year.

The statistical evaluation of mortality in the mouse study indicated that there was a significant increasing trend in males and no differences in females with incremental doses of acetochlor.

In male mice there was a significant positive trend in pulmonary adenomas and in the combined pulmonary adenomas and/or carcinomas. The males also had a significant difference in the pair-wise comparisons of controls and the highest dose group in pulmonary adenomas, combined pulmonary adenomas and/or carcinomas and in combined hepatocytic adenomas and/or carcinomas.

The female mice had a significant increasing trend in combined pulmonary adenomas and/or carcinomas. The females also had a significant difference in the pair-wise comparison of controls and the highest dose in pulmonary adenomas.

The statistical evaluation of mortality in the rats indicated that there was no evidence of increase in either sex, with incremental doses of acetochlor.

Both male and female rats had significant increasing trends in nasal epithelium adenomas, combined epithelium adenomas and/or carcinomas, thyroid follicular adenomas, and in combined thyroid follicular adenomas and/or carcinomas.

Both sexes of rats had a significant difference in the pair-wise comparison of controls and the highest dose group in nasal epithelium adenomas and in the combined nasal epithelium adenomas and/or carcinomas. The females also had a significant difference in the comparison of controls and the highest dose in thyroid follicular adenomas and in the combined thyroid follicular adenomas and/or carcinomas.

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Background

The 78 week feeding study in CD-1 mice was conducted by Life Science Research Ltd. and issued in June,1989 for ICI Americas Inc. (SC-5676, MRID no.415651-19).

The study design allocated in a random manner, groups of 50 male/female mice to dose levels of 0, 10, 100 and 1000 ppm. of acetochlor for the entire length of the study. An additional 10 mice of each sex were sellected for a 52 week interim sacrifice for each of the previously mentioned dose groups.

The 2-year feeding study in Sprague-Dawley CD rats was conducted by Life Science Research Ltd. and issued in March,1988 for ICI Central Toxicology Laboratory (SC-5676, MRID no.415920-04).

The study design allocated in a random manner, groups of 50 male/female rats to dose levels of 0, 18, 175 and 1750 ppm. of acetachlor for 104 weeks. In addition, an extra 10 animals were treated at 18 and 175 dose levels for 52 weeks as well as another group of 20 male/female at the 0 and 1750 ppm. dose levels.

Survival Analysis

Male mice had a statistically significant increasing trend in mortality with dose increments of acetochlor (Table 1). Females had no significant mortality differentials with incremental of acetochlor (Table 2).

Male rats had a significant decreasing trend in mortality with dose increments of acetochlor (Table 3). Females had no significant mortality differences with increasing doses of acetochlor (Table 4).

The statistical evaluation of mortality in both mice and rats was based upon the Thomas, Breslow and Gart computer program.

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Tumor Analysis

Male mice had a significant increasing trend in pulmonary adenomas and in the combined pulmonary adenomas and/or carcinomas (p=.007 and p=.018 respectively). The males also had a significant (p=.010) difference in the pair-wise comparison of controls and the highest dose group in pulmonary adenomas as well as a significant (p=.049) difference in the pulmonary combined adenomas and/or carcinomas (Table 6). The males also had a significant (p=.031) diference in the pair-wise comparison of controls and the highest dose group in hepatocytic combined andenomas and/or carcinomas (Table 5).

Since there were statistically significant survival differences among the various doses, the above statistical analysis of tumor rates was based upon Peto's Prevalence tests for trend and also for the pair-wise comparisons of each dose group with controls.

Female mice had a significant (p=.034) difference in the pair-wise comparison of controls and the highest dose group in pulmonary adenomas (Table 7). This analysis was based on Fisher's Exact test, since female mice had no significant differential mortality with dose increments of acetochlor.

Male rats had a significantly (p=.000) increasing trend in nasal epithelium adenomas and in the combined nasal epithelium adenomas and/or carcinomas. Males also had significant (p=.000) differences in the pair-wise comparison of controls and the highest dose group in both, the nasal epithelium adenomas and the combined nasal epithelium adenomas and/or carcinomas (Table 8). In addition, the males had significant increasing trend in thyroid follicular adenomas and in the combined thyroid follicular adenomas and/or carcinomas (p=.042 and p=.026 respectively - Table 9).

Since the male rats has significant survival differences with dose increments of acetochlor, the above statistical analysis was based on the Peto Prevalence Test for trend and the pair-wise comparisons of controls and each of the given doses.

Female rats had significantly (p=.000) increasing trends in nasal epithelium adenomas and in the combined nasal epithelium adenomas and/or carcinomas. Females also had significant (p=.000) differences in the pair-wise comparison of controls and the highest dose group in both, the nasal epithelium adenomas and in the combined nasal epithelium adenomas and/or carcinomas (Table 11). Females also had a significantly increasing trend in thyroid follicular adenomas and in the combined thyroid follicular adenomas and/or carcinomas (p=.008 and p=.003 respectively). In addition, the female rats also had significant differences in the pair-wise comparison of controls and the highest dose group in thyroid follicular adenomas and in the combined thyroid follicular adenomas and/or carcinomas (p=.044 and p=.022 respectively - Table 12).

Since female rats had no significant mortality changes with increasing doses of acetochlor, the above statistical analysis was based upon the Cochran-Armitage Trend test and Fisher's Exact test for the pair-wise comparisons of each dose level and the controls.

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

	Weeks				
Dose (ppm)	1-26	27-52	53[a]	53-79[c]	Total
0	0/60	4/60	9/56	7/47	11/51(22)*
10	0/60	1/60	11[b]/59	9/48	10/49(20)
100	0/60	3/60	10/57	11/47	14/50(28)
1000	3/60	3/57	9/54	11/45	17/51(33)

[+] 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] includes one animal sacrificed at week 69.
[c] Final sacrifice at week 79.

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 $p<.01$.

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Table 2. Acetochlor - CD-1 Mouse Study, Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks			
Dose (ppm)	1-52	53[a]	53-80[b]	Total
0	2/60	10/58	15/48	17/50(34)
10	4/60	9/56	7/47	11/51(22)
100	3/60	10/57	9/47	12/50(24)
1000	1/60	10/59	13/49	14/50(28)

+ 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 week 80.

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 3. Acetochlor - Sprague-Dawley CD Rat Study, Male Mortality Rates+ and Cox or Generalized K/W Test Results

	Weeks				
Dose (ppm)	1-52	53[a]	53-78	79-105[b]	Total
0	1/70	20/69	12/49	27/37	40/50(80)n**
18	0/60	10/60	10/50	28/40	38/50(76)
175	1/60	10/59	9/49	31/40	41/50(82)
1750	0/70	20/70	9/50	19/41	28/50(56)n*

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

n negative change

a Interim sacrifice at week 53.
b Final sacrifice at week 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 4. Acetochlor - Sprague-Dawley CD Rat Study, Female Mortality Rates+ and Cox or Generalized K/W Test Results

	Weeks				
Dose(ppm)	1-53	54[a]	54-78	79-105[c]	Total
0	3/70	18/67	9/49	20/40	32/52(62)
18	2/60	10/58	9/48	20/39	31/50(62)
175	3/60	10/57	6/47	26/41	35/50(70)
1750	4/70	19[b]/66	4/47	25/43	33/51(65)

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

a Interim sacrifice at week 54.
b includes 2 animals sacrificed at week 25.
c Final sacrifice at week 106.

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 5. Acetochlor - CD-1 Male Mice, Hepatocytic Tumor Rates+ and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
Tumors	0	10	100	1000
Adenomas (%)	2/56 (4)	5[a]/59 (8)	3/57 (5)	5/54 (9)
p=	0.120	0.126	0.343	0.087
Carcinomas (%)	1/56 (2)	3[b]/59 (5)	2/57 (4)	3/54 (6)
p=	0.211	0.154	0.249	0.117
Both (%)	3/56 (5)	8/59 (14)	5/57 (9)	8/54 (15)
p=	0.071	0.058	0.226	0.031*

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

a First adenoma observed at week 53, dose 10 ppm.
b First carcinoma observed at week 79, dose 10 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 $p<.01$.

Table 6. Acetochlor - CD-1 Male Mice, Pulmonary Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
Tumors	0	10	100	1000
Adenomas (%)	5/60 (8)	3/60 (5)	11/59 (19)	13[a]/57 (23)
p=	0.007**	0.770(n)	0.080	0.010*
Carcinomas (%)	5/60 (8)	4/60 (7)	3[b]/59 (5)	4/57 (7)
p=	0.479	0.640(n)	0.750(n)	0.570(n)
Both (%)	10/60 (17)	7/60 (12)	14/59 (24)	17/57 (30)
p=	0.018*	0.790(n)	0.188	0.049*

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

(n) negative change form control

a First adenoma observed at week 53, dose 1000 ppm.
b First carcinoma observed at week 41, dose 100 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 $p<.01$.

Table 7. Acetochlor - CD-1 Female Mice, Pulmonary Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	10	100	1000
Adenomas (%)	1/58 (2)	4[a]/59 (7)	6/58 (10)	7/60 (12)
p=	0.067	0.187	0.057	0.034*
Carcinomas (%)	4/58 (7)	0/59 (0)	2[b]/58 (3)	4/60 (7)
p=	0.146	0.057(n)	0.340(n)	0.622
Both (%)	5/58 (9)	4/59 (7)	8/58 (14)	11/60 (18)
p=	0.029*	0.489(n)	0.279	0.101

+ 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 46, dose 10 ppm.
b First carcinoma observed at week 70, dose 100 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 8. Acetochlor - Sprague-Dawley CD Male Rats, Nasal Epithelium Tumor Rates[+] and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
Tumors	0	18	175	1750
Adenomas (%)	0/69 (0)	0/59 (0)	0/59 (0)	35[a]/70 (50)
p=	0.000**	1.000	1.000	0.000**
Carcinomas (%)	0/69 (0)	0/59 (0)	0/59 (0)	2[b]/70 (3)
p=	0.073++	1.000	1.000	0.166
Both (%)	0/69 (0)	0/59 (0)	0/59 (0)	37/70 (53)
p=	0.000**	1.000	1.000	0.000**

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

++ Exact trend test result.

a First adenoma observed at week 53, dose 1750 ppm.
b First carcinoma observed at week 105, dose 1750 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 $p<.01$.

Table 9. Acetochlor - Sprague-Dawley CD Male Rats, Thyroid Follicular Tumor Rates+ and Peto's Prevalence Test Results (p values)

	Dose (ppm)			
Tumors	0	18	175	1750
Adenomas	2[a]/49	1/50	2/48	5/49
(%)	(4)	(2)	(4)	(10)
p=	0.042*	0.720(n)	0.680	0.164
Carcinomas	1[b]/49	3/50	0/48	3/49
(%)	(2)	(6)	(0)	(6)
p=	0.178	0.191	0.880(n)	0.149
Both	3/49	4/50	2/48	8/49
(%)	(6)	(8)	(4)	(16)
p=	0.026*	0.427	0.660(n)	0.060

+ 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 71, dose 0.
b First carcinoma observed at week 83, dose 0.

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 10. Acetochlor - Sprague-Dawley CD Male Rats, Malignant Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	18	175	1750
Femur; Chondroma (%)	0/49 (0)	0/48 (0)	0/48 (0)	1[a]/49 (2)
p=	0.253	1.000	1.000	0.500
Stomach; Basal Cell (%)	0/48 (0)	0/50 (0)	0/49 (0)	1[b]/49 (2)
p=	0.250	1.000	1.000	0.502

+ Number of tumor bearing animals/Number of animals examined, excluding those that died before 55 weeks.

a Chondroma of Femur observed at week 76, dose 1750 ppm.

b Basal Cell tumor of Stomach observed at week 76, dose 1750 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 11. Acetochlor - Sprague-Dawley CD Female Rats, Nasal Epithelium Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	18	175	1750
Adenomas	0/69	0/57	0/58	36[a]/63
(%)	(0)	(0)	(0)	(57)
p=	0.000**	1.000	1.000	0.000**
Carcinomas	0/69	0/57	0/58	1[b]/63
(%)	(0)	(0)	(0)	(2)
p=	0.255++	1.000	1.000	0.477
Both	0/69	0/57	0/58	37/63
(%)	(0)	(0)	(0)	(59)
p=	0.000**	1.000	1.000	0.000**

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

++ Exact Trend Test result.

a Adenoma observed at week 52, dose 1750 ppm.
b Carcinoma observed at week 90, dose 1750 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.

Table 12. Acetochlor - Sprague-Dawley CD Female Rats, Thyroid Follicular Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	18	175	1750
Adenomas (%)	1/69 (1)	1/58 (2)	3[a]/59 (5)	6/63 (10)
p=	0.008**	0.707	0.253	0.044*
Carcinomas (%)	0/69 (0)	0/58 (0)	0/59 (0)	1[b]/63 (2)
p=	0.253++	1.000	1.000	0.477
Both (%)	1/69 (1)	1/58 (2)	3/59 (5)	7/63 (11)
p=	0.003**	0.707	0.253	0.022*

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

++ Exact Trend Test result.

a First adenoma observed at week 53, dose 175 ppm.
b Carcinoma observed at week 105, dose 1750 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 $p<.01$.

Table 13. Acetochlor - Sprague-Dawley CD Female Rats, Malignant Tumor Rates+ and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
Tumors	0	18	175	1750
Femur; Chondroma (%)	0/49 (0)	0/48 (0)	0/47 (0)	1[a]/47 (2)
p=	0.246	1.000	1.000	0.490
Stomach; Basal Cell (%)	0/49 (0)	0/48 (0)	0/47 (0)	1[b]/45 (2)
p=	0.238	1.000	1.000	0.479

+ Number of tumor bearing animals/Number of animals examined, excluding those that died before 55 weeks.

a Chondroma of Femur observed at week 106, dose 1750 ppm.

b Basal Cell tumor of Stomach observed at week 105, dose 1750 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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