CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-938**

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA20-938
Name of Drug: Mobic (meloxicam 3.75 mg, 7.5 mg, and 15 mg once daily)
Applicant: Boehringer Ingelheim Pharmaceuticals
Indication: Treatment of Signs and Symptoms of Osteoarthritis
Documents Reviewed: Statistical Section of NDA20-938 Dated 12/16/99 by CDER
Reviewer: Laura Lu, Ph.D.
Date of Review: 8/24/99

I. Introduction

NDA20-938 has been submitted for approval of Mobic (meloxicam) for the treatment of signs and symptoms of osteoarthritis (OA). A total of 7 phase III clinical trials (Studies 107.043, 107.044, 107.045, 107.063, 107.153, 107.154 and 107.181) was conducted to evaluate the safety and efficacy of Mobic. This review will concentrate on the placebo-controlled trial 107.181 and overview the active-controlled trials 107.043, 107.044, 107.045, 107.063, 107.153, and 107.154.

II. Study 107.181

1. Protocol

This study is a multi-center, double-blind, double-dummy, randomized, parallel-group, placebo controlled trial to compare the efficacy and safety of three doses of meloxicam (3.75 mg, 7.5 mg, and 15 mg once daily) with placebo in patients with osteoarthritis of the knee or hip. Diclofenac 100 mg (50 mg BID) was included as an active control to assess trial sensitivity.

The primary variables evaluated in this trial are: **investigator's global assessment of disease activity** (scale 0-4), **patient's global assessment of disease activity** (continuous), **patient's overall assessment of pain** (continuous), and **the western ontario and McMaster University osteoarthritis index (WOMAC)** (continuous). The secondary variables evaluated are: **the patient's assessment of pain on active movement in the target joint, pain at rest in the target joint, the patient's final global assessment of efficacy, the investigator's final global assessment of efficacy, the patient's assessment of status with regard to change in arthritic condition**, and **use of rescue medication** (acetaminophen).

A sample size of 700 was planned (140 per treatment group) to detect the anticipated differences between the medium dose meloxicam group (7.5 mg) and placebo group for each endpoint with an α level of 0.05 and a power of 80%. The anticipated differences are: 11 in the patient's VAS global assessment of disease activity, .3 in the investigator's global assessment of disease activity, and 8.3 in the patient's VAS assessment of pain. Patients were evaluated on Day 0, Weeks 2, 4, 8, and 12.

The primary analysis was intent-to-treat analysis with last-observation-carried-forward (LOCF) approach including every patient with at least one post-dose efficacy measurements. A weighted mean on treatment approach is also used to demonstrate the robustness of the result. Continuous variables, such as patient's VAS scores and WOMAC, were analyzed by ANOVA with treatment and center as factors. Categorical variables, such as investigator's global assessment of disease activity, were analyzed by rank sum test stratified by baseline assessments and center.

2. Summary of Study Report

2.1 Patient Disposition

A total of 774 patients received treatment during the trial. Of these patients, 769 were included in the ITT population: 153, 153, 156, 155, and 152 in the meloxicam 3.75 mg, meloxicam 7.5 mg, meloxicam 15 mg, placebo, and diclofenac groups, respectively. Patient disposition is presented in the following table.

		Number of Patients (% Entered)				
		Placebo	Meloxicam 3.75 mg	Meloxicam 7.5 mg	Meloxicam 15 mg	Diclofenac 100 mg
Treated		157 (99.4%)	154 (98.7%)	154 (99.4%)	156 (99.4%)	153 (100.0%)
Prematurely Discontinued						
	AE	8 (5.1%)	13 (8.3%)	11 (7.1%)	15 (9.6%)	13 (8.5%)
	Lack of Efficacy	60 (38.0%)	44 (28.2%)	26 (16.8%)	25 (15.9%)	16 (10.5%)
	Administrative/ Other Reason	9 (5.7%)	8 (5.1%)	11 (7.1%)	5 (3.2%)	9 (5.9%)
	Total Discontinued	77 (48.7%)	65 (41.7%)	48 (31.0%)	45 (28.7%)	38 (24.8%)
Completed		80 (50.6%)	89 (57.1%)	106 (68.4%)	111 (70.7%)	115 (75.2%)
ITT Patients		155 (98.1%)	153 (98.1%)	153 (98.7%)	156 (99.4%)	152 (99.3%)

2.2 Demographics and Baseline Characteristics

The treatment groups are similar in the distribution of gender, race, age, weight, height, target joint, duration of OA and total duration of NSAIDs use. The detailed information is in Table 1-2 in Appendix A.

2.3 Efficacy Results

The following results are from ITT population by last observation carried forward approach, which is similar to the results by weighted mean on treatment approach.

Primary Endpoints

For all of the primary efficacy endpoints (investigator's global assessment of disease activity, patient's global assessment of disease activity, patient's overall assessment of pain, and the WOMAC Index), meloxicam in doses of 15 mg and 7.5 mg was statistically more efficacious than placebo. The meloxicam 3.75 mg group did not separate

significantly from the placebo group for all of the primary efficacy endpoints except for patient's global assessment of disease activity. Diclofenac was significantly more efficacious than placebo for all of the primary efficacy endpoints and was numerically better than the meloxicam groups in investigator's global assessment of disease activity, patient's global assessment of disease activity, and patient's overall assessment of pain. The P-values and confidence intervals for the primary endpoints are summarized below. Detailed results are in Tables 3-9 in Appendix A.

P-values (Confidence Intervals) of Treatment Groups vs. Placebo

Endpoints	Meloxicam 3.75 mg vs. Placebo	Meloxicam 7.5 mg vs. Placebo	Meloxicam 15 mg vs. Placebo	Diclofenac 100 mg vs. Placebo
Investigator's Global[1]	0.817	<0.001	0.002	<0.001
Patient's Global[2]	0.016 (-13.5, -1.4)	0.001 (-15.0, -3.9)	0.001 (-16.3, -4.3)	<0.001 (-20.1, -8.0)
Patient's Overall Assessment of Pain[2]	0.067 (-12.2, 0.4)	0.005 (-15.5, -2.9)	0.002 (-16.0, -3.5)	<0.001 (-18.7, -6.0)
WOMAC Index[2]	0.063 (-8.2, 0.2)	0.018 (-9.4, -0.9)	<0.001 (-12.9, -4.5)	<0.001 (-15.2, -6.8)

[1] P-values for Investigator's Global are from rank sum test stratified by baseline scores, no confidence intervals for mean are provided by this method.

[2] P-values for Patient's Global, Patient's Overall Assessment of Pain and WOMAC Index are from main effects model with factors for treatment, target joint, and center. Confidence intervals are for difference of treatment LSMEANs (a negative difference means more improvement) from ANOVA.

Secondary Endpoints

The meloxicam 15 mg group and the meloxicam 7.5 mg group were statistically significant better than the placebo group (all p-values less than .05) in all secondary endpoints (patient's assessment of pain on active movement in the target joint, patient's assessment of pain at rest in the target joint, patient's final global assessment of efficacy, patient's evaluation with regard to change in arthritic function, investigator's final global assessment of efficacy, and use of rescue medication, WOMAC subscores in pain, stiffness and physical function). The diclofenac group was also statistically significant better than the placebo group in all secondary endpoints.

III. Active-controlled Trials

1. Protocol

Studies 107.043, 107.044, 107.045, 107.063, 107.153, and 107.154 are active controlled trials in demonstrating the equivalence between the meloxicam groups (7.5 mg, 15 mg, and 30 mg once daily) and other NSAIDS such as piroxicam (20 mg once daily) and diclofenac (100 mg once daily). The important features of the trial protocols are summarized in the table below.

Study	Duration	Treatment Groups (N)	Core Category Endpoints	Statistical Methods
107.043	6 weeks	meloxicam 15 mg (129) meloxicam 30 mg[1] (29) piroxicam 20 mg (127)	1. pain on movement 2. pain at rest 3. investigator's global assessment of disease activity 4. patient's global assessment of disease activity	confidence intervals for treatment differences measured by LSMEAN and Q-statistic
107.044	6 weeks	meloxicam 15 mg (128) meloxicam 30 mg[1] (10) diclofenac 100 mg (130)	same as that in 107.043[2]	same as that in 107.043
107.045	6 months	meloxicam 15 mg (306) piroxicam 20 mg (149)	1. pain on movement 2. patient's assessment of pain 3. investigator's global assessment of disease activity 4. patient's global assessment of disease activity	same as that in 107.043
107.063	6 months	meloxicam 15 mg (169) diclofenac 100 mg (167)	same as that in 107.045	same as that in 107.043
107.153	1 months	meloxicam 7.5 mg (4635) diclofenac 100 mg (4668)	same as that in 107.043[2]	same as that in 107.043
107.154	1 months	meloxicam 7.5 mg (4320) piroxicam 20 mg (4336)	same as that in 107.043[2]	same as that in 107.043

[1] Meloxicam 30 mg group discontinued due to GI toxicity

[2] Investigator's global assessment of disease activity and patient's global assessment of disease activity may be evaluated by different methods in different studies. See details in study results.

5. Summary of Study Report

5.1 Patient Disposition

Patients' Disposition in the intention-to-treat population are listed in the following table. The dropout rates of meloxicam due to lack of efficacy range from 2%-4%, which are comparable to those of active comparators, and those due to adverse events range from 5%-15%, which are generally less than those of active comparators.

Study	Treatment Groups	Completed	Total Discontinued	Discontinued Due To Adverse Events	Discontinued Due To Lack Of Efficacy	Discontinued Due To Other Reasons
107.043	Meloxicam 15 mg Piroxicam	113 (88%) 112 (88%)	15(12%) 15(12%)	12(9%) 10(8%)	2(2%) 4(3%)	1(1%) 1(1%)
107.044	Meloxicam 15 mg Diclofenac	99 (79%) 103(80%)	26(21%) 26(20%)	19(15%) 23(18%)	5(4%) 3(2%)	2(2%) 0(0%)
107.045	meloxicam 15 mg piroxicam	223(73%) 98(66%)	83(27%) 51(34%)	45(15%) 28(19%)	9(3%) 3(2%)	29(9%) 20(13%)
107.063	meloxicam 15 mg diclofenac	124(73%) 110(67%)	45(27%) 54(33%)	21(12%) 30(18%)	7(4%) 7(4%)	17(10%) 17(10%)
107.153	meloxicam 7.5 mg diclofenac	4186(91%) 4137(89%)	402(9%) 500(11%)	235(5%) 345(7%)	74(2%) 48(1%)	93(3%) 107(2%)
107.154	meloxicam 7.5 mg piroxicam	3853(90%) 3812(89%)	420(10%) 475(11%)	243(6%) 290(7%)	74(2%) 67(2%)	103(2%) 118(3%)

2.2 Efficacy Results

The efficacy of meloxicam was evaluated by comparing with active comparators in mainly the following three domains: Pain, Investigator's Global Evaluation and Patient's Global Evaluation. In all six active controlled trials, no statistically significant difference was detected between meloxicam and the active comparator in any primary endpoints except that in trial 107.153, meloxicam 7.5 mg was significantly worse than diclofenac 100 mg in Patient's Global Evaluation ($p=0.023$). In all trials, the limits of confidence intervals for the differences between meloxicam and the active comparator in primary endpoints are within the calculated delta (10% observed range), and most of them are within the Delphi delta (defined by Bellamy et al.) except those for Duration of Stiffness in trial 107.45 and 107.63. The results for primary endpoints for each trial are summarized in Tables 10-15 in Appendix A.

IV. Reviewer's Comments

1. Use of Rescue Medication

In trial 107.181, the fact that the use of rescue medication reduced significantly more ($p<0.01$) in the two meloxicam dose groups than in the placebo group support the efficacy of meloxicam. Another way to examine the influence of rescue medication use to efficacy outcome is to analyzed the primary endpoints by an ANOVA model with centers as factor and the change of rescue medication use from baseline as a covariate. The result shows that the coefficients in the ANOVA model for the change of rescue medication use are significant (<0.0003) and positive, which means the efficacy outcome is better when the use of rescue medication is reduced. This result confirms that the efficacy of meloxicam is not due to use of rescue medication.

2. Differences Between the Results of Placebo-controlled and Active-controlled Trials

In the placebo controlled trial 107.181, the discontinuation rates due to lack of efficacy (16.8% for meloxicam 7.5 mg, 15.9% for meloxicam 15 mg, and 10.5% for diclofenac 100 mg) are higher than those in the active controlled trials (2% for meloxicam 7.5 mg, 2-4% for meloxicam 15 mg, and 1-4% for diclofenac 100 mg). In trial 107.181, declofenac 50 mg is numerically better than meloxicam dose groups in investigator's global assessment of disease activity, patient's global assessment of disease activity, and patient's overall assessment of pain, but the active controlled trials did not show such a trend.

V. Final Conclusion

Study 107.181 demonstrated the superiority of meloxicam 7.5 mg and meloxicam 15 mg over placebo, but did not demonstrate the superiority of meloxicam 3.75 mg over placebo. The active controlled trials (107.043, 107.044, 107.045, 107.63, 107.153, 107.154) showed no statistically significant differences between meloxicam and active comparators (meloxicam 7.5 mg and piroxicam 20 mg, meloxicam 15 mg and piroxicam 20 mg. meloxicam 7.5 mg and diclofenac 100 mg, meloxicam 15 mg and diclofenac 100 mg) in primary endpoints, and the limits of 95% confidence intervals for the difference between meloxicam and active comparators are within 10% of the observed range of primary endpoints. However, it is unclear whether the 10% observed range is appropriate for defining equivalence between treatments. In addition, the active-controlled trials did not include a placebo group and therefore poses difficulty in evaluating equivalence between treatments.

/S/

Laura Lu, Ph.D.
Mathematical Statistician

Concur:

/S/ 8/24/99

Stan Lin, Ph.D.
Team Leader

/S/ 8/24/99

Mo Huque
Division Director

CC:

NDA20-938
HFD-550/Johnson
HFD-550/Lewin
HFD-550/Hyde
HFD-550/Midthun
HFD-550/Div. File
HFD-725/Lu
HFD-725/Lin ST.
HFD-725/Huque
HFD-725/Div. File

Appendix A

Table 1. Demographics (Study 107.181)

		Treatment Group				
		Placebo (N=157)	Meloxicam 3.75 mg (N=154)	Meloxicam 7.5 mg (N=154)	Meloxicam 15 mg (N=156)	Diclofenac 100 mg (N=153)
Sex	Male	55 (35.0%)	51 (33.1%)	57 (37.0%)	56 (35.9%)	49 (32.0%)
	Female	102 (65.0%)	103 (66.9%)	97 (63.0%)	100 (64.1%)	104 (68.0%)
Race	Caucasian	143 (91.1%)	139 (90.3%)	141 (91.6%)	140 (89.7%)	136 (88.9%)
	Negroid	10 (6.4%)	9 (5.8%)	8 (5.2%)	7 (4.5%)	13 (8.5%)
	Mongoloid	4 (2.5%)	6 (3.9%)	5 (3.2%)	9 (5.8%)	4 (2.6%)
Age (yrs.)	< 40	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	40 – 50	24 (15.3%)	23 (14.9%)	20 (13.0%)	11 (7.1%)	17 (11.1%)
	51 – 60	44 (28.0%)	39 (25.3%)	48 (31.2%)	46 (29.5%)	48 (31.4%)
	61 – 70	50 (31.8%)	55 (35.7%)	49 (31.8%)	58 (37.2%)	45 (29.4%)
	71 – 80	34 (21.7%)	32 (20.8%)	35 (22.7%)	34 (21.8%)	41 (26.8%)
	> 80	5 (3.2%)	4 (2.6%)	2 (1.3%)	7 (4.5%)	1 (0.7%)
	Mean ± SD	62.3 ± 10.8	62.3 ± 10.5	62.4 ± 10.2	64.3 ± 9.9	63.0 ± 10.0
Weight (lbs.)	Mean ± SD	197.4 ± 55.2	201.1 ± 49.2	203.1 ± 48.5	194.2 ± 47.9	204.4 ± 47.0
Height (in.)	Mean ± SD	65.9 ± 4.2	65.9 ± 4.2	66.2 ± 4.2	66.0 ± 3.9	65.8 ± 4.2

Table 2. Baseline Characters (Study 107.181)

		Treatment Group				
		Placebo (N=157)	Meloxicam 3.75 mg (N=154)	Meloxicam 7.5 mg (N=154)	Meloxicam 15 mg (N=156)	Diclofenac 100 mg (N=153)
Target Joint	Hip	25 (15.9%)	24 (15.6%)	31 (20.1%)	25 (16.0%)	34 (22.2%)
	Knee	132 (84.1%)	130 (84.4%)	123 (79.9%)	131 (84.0%)	119 (77.8%)
Other Involved Joint		139 (88.5%)	141 (91.6%)	140 (90.9%)	138 (88.5%)	136 (88.9%)
Duration of OA (yrs.)	≤ 5 years	73 (46.5%)	73 (47.4%)	73 (47.4%)	89 (57.1%)	74 (48.4%)
	> 5 years	84 (53.5%)	81 (52.6%)	81 (52.6%)	67 (42.9%)	79 (51.6%)
	Mean ± SD	8 ± 7.2	9 ± 9.4	8 ± 8.4	7 ± 7.8	9 ± 8.3
Total duration of Prior NSAID Use (days)	N	155	154	151	155	149
	Mean ± SD	1455 ± 1590.8	1512 ± 1818.9	1404 ± 1573.1	1372 ± 1591.2	1437 ± 1753.6

Table 3. Results for Investigator's Global Assessment of Disease Activity (Study 107.181)

Q: Considering the patient's present function, how would you judge his or her disease activity?		Treatment Group				
		Placebo (N=155)	Meloxicam 3.75 mg (N=153)	Meloxicam 7.5 mg (N=153)	Meloxicam 15 mg (N=156)	Diclofenac 100 mg (N=152)
Week 0 (Baseline)	None	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mild	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	63 (40.6%)	63 (41.2%)	59 (38.6%)	70 (44.9%)	54 (35.5%)
	Severe	82 (52.9%)	78 (51.0%)	84 (54.9%)	76 (48.7%)	81 (53.3%)
	Very Severe	10 (6.5%)	11 (7.2%)	10 (6.5%)	10 (6.4%)	17 (11.2%)
Final Visit (LOCF)	None	9 (5.8%)	9 (5.9%)	11 (7.2%)	12 (7.7%)	8 (5.3%)
	Mild	44 (28.4%)	51 (33.3%)	66 (43.1%)	73 (46.8%)	83 (54.6%)
	Moderate	56 (36.1%)	54 (35.3%)	57 (37.3%)	50 (32.1%)	38 (25.0%)
	Severe	40 (25.8%)	31 (20.3%)	17 (11.1%)	14 (9.0%)	20 (13.2%)
	Very Severe	6 (3.9%)	8 (5.2%)	2 (1.3%)	7 (4.5%)	3 (2.0%)
P-value[1]			0.817	<0.001	0.002	<0.001

[1] P-value for treatment against placebo by rank sum test stratified by baseline scores.

Table 4. Results for Treatment Comparisons for Patient's Global Assessment of Disease Activity (Study 107.181)

Patient's Global Assessment of Disease Activity (VAS)[4]	Treatment Contrast	LSMEAN Difference[2]	95% Confidence Interval for LSMEAN Difference	p-value[3] for LSMEAN Difference
Final Visit (LOCF)[1]	Meloxicam 15 mg vs. Placebo	-10.3	(-16.3, -4.3)	0.001
	Meloxicam 7.5 mg vs. Placebo	-10.0	(-16.0, -3.9)	0.001
	Meloxicam 3.75 mg vs. Placebo	-7.5	(-13.5, -1.4)	0.016
	Diclofenac 100 mg vs. Placebo	-14.1	(-20.1, -8.0)	<0.001

[1] Main effects model with factors for treatment, target joint, and center.
[2] Difference of treatment LSMEANs from ANOVA. A negative difference means more improvement.
[3] P-value for treatment against placebo
[4] 100-mm visual analogue scale: 0 = No disease activity, 100 = Most severe disease activity.

Table 5. Results for Treatment Comparisons for Patient's Overall Assessment of Pain (Study 107.181)

Patient's Total Assessment of Pain (VAS)[4]	Treatment Contrast	LSMEAN Difference[2]	95 % Confidence Interval for LSMEAN Difference	p-value[3] for LSMEAN Difference
Final Visit (LOCF)	Meloxicam 15 mg vs. Placebo	-9.7	(-16.0, -3.5)	0.002
	Meloxicam 7.5 mg vs. Placebo	-9.2	(-15.5, -2.9)	0.005
	Meloxicam 3.75 mg vs. Placebo	-5.9	(-12.2, 0.4)	0.067
	Diclofenac 100 mg vs Placebo	-12.4	(-18.7, -6.0)	<0.001

[1] Main effect model with factors for treatment, target joint, and center.
[2] Difference of treatment LSMEANs from ANOVA. A negative difference means more improvement.
[3] P-value for treatment against placebo.
[4] 100-mm visual analogue scale: 0 = No pain, 100 = Unbearable pain.

Table 6. Results for Treatment Comparisons for the Total Score (WOMAC Index) (Study 107.181)

Total Score Change from Baseline	Treatment Contrast	LSMEAN Difference[2]	95% Confidence Interval for LSMEAN Difference	p-value[3] for LSMEAN Difference
Final Visit (LOCF)	Meloxicam 15 mg vs. Placebo	-8.7	(-12.9, -4.5)	<0.001
	Meloxicam 7.5 mg vs. Placebo	-5.1	(-9.4, -0.9)	0.018
	Meloxicam 3.75 mg vs. Placebo	-4.0	(-8.2, 0.2)	0.063
	Diclofenac 100 mg vs. Placebo	-11.0	(-15.2, -6.8)	<0.001

[1] Main effects model with factors for treatment, target joint, and center.
[2] Difference of treatment LSMEANs from ANOVA. A negative difference means more improvement.
[3] P-value for treatment against placebo.
[4] Weighted mean of all post-baseline assessments.

Table 7. Results for Treatment Comparisons for Pain (WOMAC Index) (Study 107.181)

Pain Change from Baseline	Treatment Contrast	LSMEAN Difference[2]	95% Confidence Interval for LSMEAN Difference	p-value[3] for LSMEAN Difference
Final Visit (LOCF)	Meloxicam 15 mg vs. Placebo	-2.3	(-3.3, -1.4)	<0.001
	Meloxicam 7.5 mg vs. Placebo	-1.2	(-2.2, -0.2)	0.017
	Meloxicam 3.75 mg vs. Placebo	-0.5	(-1.4, 0.5)	0.327
	Diclofenac 100 mg vs. Placebo	-2.3	(-3.2, -1.3)	<0.001

[1] Main effects model with factors for treatment, target joint, and center.
[2] Difference of treatment LSMEANs from ANOVA. A negative difference means more improvement.
[3] P-value for treatment against placebo.

Table 8. Results for Treatment Comparisons for Stiffness (WOMAC Index) (Study 107.181)

Stiffness Change from Baseline	Treatment Contrast	LSMEAN Difference[2]	95% Confidence Interval for LSMEAN Difference	p-value[3] for LSMEAN Difference
Final Visit (LOCF)	Meloxicam 15 mg vs. Placebo	-1.0	(-1.4, -0.6)	<0.001
	Meloxicam 7.5 mg vs. Placebo	-0.7	(-1.1, -0.3)	0.001
	Meloxicam 3.75 mg vs. Placebo	-0.6	(-1.0, -0.2)	0.004
	Diclofenac 100 mg vs. Placebo	-1.1	(-1.5, -0.7)	<0.001

[1] Main effects model with factors for treatment, target joint, and center.
[2] Difference of treatment LSMEANs from ANOVA. A negative difference means more improvement.
[3] P-value for treatment against placebo.

Table 9. Results for Treatment Comparisons for Physical Function (WOMAC Index) (Study 107.181)

Physical Function Change from Baseline	Treatment Contrast	LSMEAN Difference[2]	95% Confidence Interval for LSMEAN Difference	p-value[3] for LSMEAN Difference
Final Visit (LOCF)	Meloxicam 15 mg vs. Placebo	-5.4	(-8.4, -2.4)	<0.001
	Meloxicam 7.5 mg vs. Placebo	-3.2	(-6.2, -0.1)	0.040
	Meloxicam 3.75 mg vs. Placebo	-2.9	(-6.0, 0.1)	0.059
	Diclofenac 100 mg vs. Placebo	-7.7	(-10.7, -4.6)	<0.001

[1] Main effects model with factors for treatment, target joint, and center.
[2] Difference of treatment LSMEANs from ANOVA. A negative difference means more improvement.
[3] P-value for treatment against placebo.

Table 10. Primary Efficacy Results (Study 107.043)

Core Category Endpoint	Visit	Meloxicam 15 mg vs Piroxicam 20 mg				
		LSMEAN Difference[1]	95% CI[2]	Delphi Delta[3]	Calculated Delta[4]	p-value
Pain Pain on Movement (VAS)[5] Change from Baseline	Final Visit (LOCF)	-3.1	-9.0, 2.8	17.5	11.9	0.302
Pain Pain at Rest (VAS)[5] Change from Baseline	Final Visit (LOCF)	-0.8	-6.6, 5.0	10.5	17.3	0.793
Objective Investigator Lequesne Index of Severity (total score) Change from Baseline	Final Visit (LOCF)	-0.3	-1.2, 0.5	3.0	2.7	0.415
Patient Global Global Efficacy (VAS)[6]	Final Visit (LOCF)	-2.9	-9.3, 3.5	15.0	10.0	0.375

[1] Difference of treatment LSMEANs (Meloxicam 15 mg – Piroxicam 20 mg) from main effect model with factors for treatment and center. A negative difference means more improvement.
[2] 95% Confidence Interval for LSMEAN difference.
[3] Defined by Bellamy et al. The value for the Lequesne index was established using the Knee index.
[4] 10% of overall observed range.
[5] 100 mm visual analogue scale: 0 = no pain, 100 = unbearable pain.
[6] 100 mm visual analogue scale: 0 = excellent, 100 = useless.

Table 11. Primary Efficacy Results (Study 107.044)

Core Category Endpoint	Visit	Meloxicam 7.5 mg vs Diclofenac 100 mg SR				
		LSMEAN Difference[1]	95% CI[2]	Delphi Delta[3]	Calculated Delta[4]	p-value
Pain Pain on Movement (VAS)[5] Change from Baseline	Final Visit (LOCF)	-3.7	-9.1, 1.8	17.5	14.0	0.184
Pain Pain at Rest (VAS)[5] Change from Baseline	Final Visit (LOCF)	-1.2	-6.7, 4.4	10.5	13.9	0.676
Objective/ Investigator Lequesne Index of Severity (total score) Change from Baseline	Final Visit (LOCF)	-0.2	-1.0, 0.5	3.0	2.0	0.544
Patient Global Efficacy (VAS)[6]	Final Visit (LOCF)	-5.3	-12.1, 1.4	15.0	10.0	0.119

[1] Difference of treatment LSMEANs (Meloxicam 15 mg – Diclofenac 100 mg) from main effect model with factors for treatment and center. A negative difference means more improvement.
[2] 95% Confidence Interval for LSMEAN difference
[3] Defined by Bellamy et al. The value for the Lequesne index was established using the Knee index.
[4] 10% of overall observed range.
[5] 100 mm visual analogue scale: 0 = no pain, 100 = unbearable pain.
[6] 100 mm visual analogue scale: 0 = excellent, 100 = useless.

Table 12. Primary Efficacy Results (Study 107.045)

Core Category Endpoint	Visit	Meloxicam 15 mg vs Piroxicam 20 mg				
		LSMEAN Difference[1]	95% CI[2]	Delphi Delta[3]	Calculated Delta[4]	p-value
Pain Overall Pain (VAS)[5] Change from Baseline	Final Visit (LOCF)	-4.1	-8.6, 0.5	20.0	17.0	0.078
Pain Pain on Movement (VAS)[5] Change from Baseline	Final Visit (LOCF)	-2.1	-6.6, 2.5	17.5	13.2	0.376
Objective/ Investigator Quality of Life (total score) Change from Baseline	Final Visit (LOCF)	0.1	-0.5, 0.8	-	2.5	0.689
Patient Global Global Efficacy (VAS)[6]	Final Visit (LOCF)	0.1	-4.4, 4.7	15.0	10.0	0.952
Other Duration of Stiffness (minutes) Change from Baseline	Final Visit (LOCF)	-5.4	-30.0, 19.2	20.0	283.5	0.665

[1] Difference of treatment LSMEANs (Meloxicam 15 mg – Piroxicam 20 mg) from main effect model with factors for treatment and center. A negative difference means more improvement.
[2] 95% Confidence Interval for LSMEAN difference.
[3] Defined by Bellamy et al. The value for the Lequesne index was established using the Knee index.
[4] 10% of overall observed range.
[5] 100 mm visual analogue scale: 0 = no pain, 100 = unbearable pain.
[6] 100 mm visual analogue scale: 0 = excellent, 100 = useless.

Table 13. Primary Efficacy Results (Study 107.063)

Core Category Endpoint	Visit	Meloxicam 7.5 mg vs Diclofenac SR 100 mg				
		LSMEAN Difference[1]	95% CI[2]	Delphi Delta[3]	Calculated Delta[4]	p-value
Pain Overall Pain (VAS)[5] Change from Baseline	Final Visit (LOCF)	1.9	-3.5, 7.3	20.0	14.5	0.485
Pain Pain on Movement (VAS)[5] Change from Baseline	Final Visit (LOCF)	2.2	-3.4, 7.9	17.5	13.9	0.436
Objective/ Investigator Quality of Life (total score) Change from Baseline	Final Visit (LOCF)	0.0	-0.8, 0.8	--	2.5	1.000
Patient Global Global Efficacy (VAS)[6]	Final Visit (LOCF)	3.3	-2.6, 9.2	15.0	10.0	0.274
Other Duration of Stiffness (minutes) Change from Baseline	Final Visit (LOCF)	-13.1	-37.5, 11.2	20.0	171.0	0.290

[1] Difference of treatment LSMEANs (Meloxicam 15 mg – Diclofenac 100 mg) from main effect model with factors for treatment and center. A negative difference means more improvement.
[2] 95% Confidence Interval for LSMEAN difference
[3] Defined by Bellamy et al. The value for the Lequesne index was established using the Knee index.
[4] 10% of overall observed range.
[5] 100 mm visual analogue scale: 0 = no pain, 100 = unbearable pain.
[6] 100 mm visual analogue scale: 0 = excellent, 100 = useless.

Table 14. Primary Efficacy Results (Study 107.153)

Core Category Endpoint	Meloxicam 7.5 mg vs Diclofenac 100 mg SR				
	LSMEAN Difference[1]	95% CI[2]	Predefined Delta[3]	Calculated Delta[4]	p-value
Pain					
Pain on Movement (VAS) Change from baseline	1.8	-1.2, 4.8	17.5	14.3	0.242
Pain at Rest (VAS) Change from baseline	-1.2	-4.1, 1.8	10.5	17.9	0.440
Objective/Investigator					
Global Efficacy by Investigator (four point scale)	0.09	-0.01, 0.20	0.80	0.30	0.090
Patient Global					
Global Efficacy by Patient (four point scale)	0.13	0.02, 0.25	0.80	0.30	0.023
Patient Status (three point scale)	0.03	-0.04, 0.11	0.67	0.20	0.370
Patient Assessment of Arthritic Condition Change from baseline (four point scale)	0.04	-0.08, 0.16	0.80	0.50	0.515

[1] Difference of treatment LSMEANs (Meloxicam 15 mg – Diclofenac 100 mg) from main effect model with factors for treatment and center. A negative difference means more improvement.
[2] 95% Confidence Interval for LSMEAN difference
[3] Defined by Bellamy et al. The value for the Lequesne index was established using the Knee index.
[4] 10% of overall observed range.

Table 15. Primary Efficacy Results (Study 107.154)

Core Category Endpoint	Meloxicam 7.5 mg vs Piroxicam 20 mg				
	LSMEAN Difference[1]	95% CI[2]	Predefined Delta[3]	Calculated Delta[4]	p-value
Pain					
Pain on Movement (VAS) Change from baseline	2.7	-0.9, 6.3	17.5	16.2	0.138
Pain at Rest (VAS) Change from baseline	1.0	-2.6, 4.6	10.5	16.3	0.591
Objective/Investigator Global Efficacy by Investigator (four point scale)	0.06	-0.06, 0.18	0.80	0.30	0.325
Patient Global Global Efficacy by Patient (four point scale)	0.02	-0.10, 0.15	0.80	0.30	0.707

[1] Difference of treatment LSMEANs (Meloxicam 15 mg – Piroxicam 20 mg) from main effect model with factors for treatment and center. A negative difference means more improvement.
[2] 95% Confidence Interval for LSMEAN difference
[3] Defined by Bellamy et al. The value for the Lequesne index was established using the Knee index.
[4] 10% of overall observed range.

STATISTICAL REVIEW AND EVALUATION
(Carcinogenicity Review)

NDA #: 20-938

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

NAME OF DRUG: MOBIC® (meloxicam) Tablets, 7.5 mg

DOCUMENTS REVIEWED: Volumes 1 through 7 of NDA 20-938. Data on Floppy Diskettes supplied by the sponsor.

REVIEWING PHARMACOLOGIST: Josie Yang, Ph.D. (HFD-550).

I. BACKGROUND

In this submission, a total of 2 animal carcinogenicity studies were included:

Study No. 3805/86: Rat Carcinogenicity Study
Study No. 4184/87: Mouse Carcinogenicity Study.

These two studies were conducted to investigate the carcinogenic potential of MOBIC® (meloxicam) Tablets when administered orally at selected dose levels for up to 104 weeks (99 weeks in female mice as approximately 73%-82% mortality was reached).

II. THE RAT STUDY (Study No. 3805/86)

IIa. Design

A 104-week study was conducted in rats to investigate the carcinogenic potential of MOBIC® (meloxicam) when administered orally. Three groups of 50 male and 50 female rats (Crl:CD BR Sprague-Dawley[redacted]) were treated with MOBIC® (meloxicam) in concentrations of 0.4 (low), 0.6 (medium) and 0.8 (high) mg/kg/day; and one control group of 100 male and 100 female rats (Crl:CD BR Sprague-Dawley[redacted]) received the standardized diet without dosing.

IIb. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis,[redacted] were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics, FDA. The results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold:
(1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and
(2) To determine the significance of a positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al. (1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 1a (male) and 1b (female) summarize the number of animals died at different time-intervals. Tables 2a and 2b summarize intercurrent mortality data for the male and female rats respectively. For the male rats, there appears to be an increased mortality in the low dose group as compared to other dose groups.

- Figures 1a and 1b depict the survival distributions for males and females respectively. For the male rats (after 70 weeks), there appears to be an increased mortality in the low dose group when compared to the other doses.

- Tables 3a and 3b display the p-values of the test of homogeneity and of positive linear trends for males and females using the test and the generalized test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test which gives equal weight to all deaths.

  The test of homogeneity and the test of linear trend yield non-significant results for the male as well as female rats.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of a positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor types were classified as fatal and non-fatal. Table 4 (Part I) displays selected organs and organ codes. Table 4 (Part II) displays tumors and tumor codes.

Following Peto et al. (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused death for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 0.4, 0.6, and 0.8 for control, low, medium, and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 0.4, 0.6 and 0.8 mg/kg of MOBIC® (meloxicam). The time-intervals used were 0-52, 53-78, 79-91, 92-104, 105 and beyond for males and females.

The tumor analysis results are displayed in the Appendix. Tables 5a and 5b describe the p-values for the test of trend based on the tumor data for males and females, respectively. The rule proposed by Haseman (1983) could be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by Lin and Rahman (1995) for trend tests was used in this review. This rule for trend tests says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of 1% or less (rare tumors) should be tested at a 0.025 significance level, otherwise (for common tumors) a 0.005 significance level should be used.

On the basis of the rule for trend tests described above, no statistically significant positive linear trend or increased incidence was detected in any of the tested tumor types.

IIc. Evaluation of Validity of the Design of Rat Study (Study No. 3805/86)

This reviewer's analyses show that for rat study, there is no statistically significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in rats, it is important to look into the following two issues as having been pointed out by Haseman (1984) in Environmental Health Perspective:

(i) Were enough animals exposed, for a sustained amount of time, to the risk of a late developing tumor?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the rats?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

(i) Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on average, approximately 50% of the animals in the high dose group survived the two-year study period.

(ii) Also, in personal communication with Dr. Karl Lin of Division of Biometrics II, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.

(iii) In addition, Chu, Cueto and Ward (1981) suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy:

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the rat carcinogenicity study in the light of the above guidelines.

Validity of Rat Study (Study No. 3805/86)

Tables 2a and 2b contain mortality rates. Survival rates can be obtained by subtracting mortality rates from 100% for male and female rats for all the dose levels and for the times: end of 52 weeks, end of 78 weeks, end of 91 weeks, and end of 104 weeks. From the survival criteria mentioned above, it can be concluded that enough numbers of rats were exposed to the drug for a sufficient amount of time in both sexes.

According to the sponsor (p. 9177, vol. 4 of 7), the maximum differences of the decreased body weight gain at the highest tested dose level of 0.8 mg/kg/day from the controls were between 7% and 8% and never exceeded the 10% limit. From the weight-gain criteria mentioned above, it can be concluded that the high dose used (0.8 mg/kg/day) may be close to the maximum tolerated dose for the both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

IId. Additional Analyses Requested by the Reviewing Pharmacologist

The reviewing pharmacologist requested the following 8 analyses for combined organs and combined tumors for males and females.

Analysis #1: All heamangioma (000200) together **for all tissues**

Analysis #2: All heamangioma (000200) + angioma (000130) + angiosarcoma (000401) together **for all tissues**

Analysis #3: All lymphoma (000270) together **for all tissues**

Analysis #4: All lymphoma (000270) + limphangioma (000260) together **for all tissues**

Analysis #5: All lipoma (000240) + fibrolipoma (000241) together **for all tissues**

Analysis #6: All sarcoma (000400) together **for all tissues**

Analysis #7: Skin (000510):

- squamous cell carcinoma (000143) + papilloma (000300) + Carcinoma (000140)
- lipoma (000240) + fibrolipoma (000241)

Mammary Gland (000320):

- Adenoma (000100) + Fibroadenoma (000102) + adenofibroma (000171)
- Carcinoma (000140)+Adenocarcinoma (000141)+Squamous cell carcinoma (000143)

Stomach (000550):

- Squamous cell carcinoma (000143) + Papilloma (000300)

Liver (000280):

- Hepatocellular Adenoma (000103) + Carcinoma (000140)

Pituitary (000410):

- Adenoma (000100) + Carcinoma (000140)
- Phaeochromocytoma (000310)

Thyroid (000610):

- Adenoma (000100) + Carcinoma (000140)
- Phaeochromocytoma (000310)

Adrenal (000100):

- Adenoma (000100) + Carcinoma (000140)
- Phaeochromocytoma (000310)

Parathyroids (000390):
- Adenoma (000100) + Carcinoma (000140)
- Phaeochromocytoma (000310)

Prostate (000430):
- Adenoma (000100) + Carcinoma (000140)

Brain (000130):
- Glioma (000190) + Ependymoma (000160)

Lung (000290):
- adenoma (000100) + adenocarcinoma (000141)

Salivary gland (000480):
- squamous cell carcinoma (000143) + carcinoma (000140)

Pancreas (000380):
- insuloma (000220) + adenoma (000100)

Testicles (000560) + Epididymides (000160):
- interstitial cell tumor (001003)

Uterus (000650):
- Carcinoma (000140)+Adenocarcinoma (000141)+Squamous cell carcinoma (000143)
- Fibroadenoma (000102) + adenofibroma (000171)

Analysis #8: Pituitary (000410) + Thyroid (000610) + Adrenal (000100) + Parathyroids (000390):
- Adenoma (000100) + Carcinoma (000140)
- Phaeochromocytoma (000310)

These analyses were performed on the available data. Results are given below. No statistically significant dose-tumor positive linear trend was detected.

Analysis #1 (Male Rats): All heamangioma (000200) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR.
For all tissues	(LLST)	IN	105-106	1	1 0 1 1	0.377	0.300	0.646
Haemangioma	(H)	IN	105-106	2	67 28 39 34			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 1 1			

Analysis #1 (Female Rats): All heamangioma (000200) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
For all tissues	(FAT)	IN	79-91	1	0 1 0 0	0.535	0.356	0.912
Haemangioma	(H)	IN	79-91	2	13 5 7 2			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0 1 0 0			

Analysis #2 (Male Rats): All heamangioma (000200) + angioma (000130) + angiosarcoma (000401) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
For all tissues	(FAT)	IN	53-78	1	1 0 0 0	0.589	0.535	0.813
Heamangioma+angioma+	(HAA)	IN	53-78	2	4 6 2 2			
angiosarcoma		IN	105-106	1	1 0 1 1			
		IN	105-106	2	67 28 39 34			
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	2 0 1 1			

Analysis #2 (Female Rats): All heamangioma (000200) + angioma (000130) + angiosarcoma (000401) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
For all tissues	(FAT)	IN	79-91	1	0 1 0 0	0.252	0.194	0.617
Heamangioma+angioma+	(HAA)	IN	79-91	2	13 5 5 2			
Angiosarcoma		FA	86	1	0 0 1 0			
		FA	86	2	85 43 40 43			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0 1 1 0			

Analysis #3 (Male Rats): All lymphoma (000270) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
For all tissues	(BLT)	IN	105-106	1	1 0 1 0	0.615	0.572	0.859
Lymphoma	(L)	IN	105-106	2	67 28 39 35			
		FA	102	1	0 1 0 0			
		FA	102	2	72 28 41 35			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	1 1 1 0			

Analysis #3 (Female Rats): All lymphoma (000270) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
For all tissues	(BLT)	IN	53-78	1	0 0 1 0	0.339	0.285	0.704
Lymphoma	(L)	IN	53-78	2	8 4 4 5			
		FA	80	1	0 1 0 0			
		FA	80	2	90 45 42 43			
Spontaneous tumor pct: <= 1% in ctrl. -		Total		-	0 1 1 0			

Analysis #4 (Male Rats): All lymphoma (000270) + limphangioma (000260) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
For All Tissues	(FAT	)	IN 92-104	1	0 2 0 0	0.141	0.122	0.226
Lymphoma+Lymphangioma	(LL	)	IN 92-104	2	12 7 5 9			
			IN 105-106	1	2 2 7 1			
			IN 105-106	2	66 26 33 34			
			FA 102	1	0 1 0 0			
			FA 102	2	72 28 41 35			
Spontaneous tumor pct: 2%	in ctrl. -	Total	-		2 5 7 1			

Analysis #4 (Female Rats): All lymphoma (000270) + limphangioma (000260) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
For All Tissues	(FAT	)	IN 53-78	1	0 0 1 0	0.102	0.082	0.201
Lymphoma+Lymphangioma	(LL	)	IN 53-78	2	8 4 4 5			
			IN 105-106	1	1 0 3 1			
			IN 105-106	2	63 34 28 34			
			FA 80	1	0 1 0 0			
			FA 80	2	90 45 42 43			
			FA 103	1	0 0 1 0			
			FA 103	2	66 36 32 36			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total	-		1 1 5 1			

Analysis #5 (Male Rats): All lipoma (000240) + fibrolipoma (000241) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
For All Tissues	(FAT	)	IN 92-104	1	0 0 0 1	0.078	0.063	0.159
Lipoma+fibrolipoma	(LL	)	IN 92-104	2	12 10 5 8			
			IN 105-106	1	1 3 2 2			
			IN 105-106	2	67 25 38 33			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total						

Analysis #5 (Female Rats): All lipoma (000240) + fibrolipoma (000241) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
For All Tissues	(FAT	)	IN 79-91	1	1 0 0 0	0.816	0.788	0.919
Lipoma+fibrolipoma	(LL	)	IN 79-91	2	12 6 7 2			
			IN 92-104	1	0 1 0 0			
			IN 92-104	2	14 5 6 6			
			IN 105-106	1	2 2 1 0			
			IN 105-106	2	62 32 30 35			
Spontaneous tumor pct: 3%	in ctrl. -	Total	-		3 3 1 0			

Analysis #6 (Male Rats): All sarcoma (000400) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
For All Tissues	(LMPST	) IN	79-91	1	2 0 0 0	0.958	0.947	0.983
Sarcoma	(S	) IN	79-91	2	10 6 2 4			
		IN	105-106	1	4 0 0 0			
		IN	105-106	2	64 28 40 35			
		FA	95	1	0 0 0 1			
		FA	95	2	78 36 44 39			
		FA	98	1	0 1 0 0			
		FA	98	2	75 35 42 37			
		FA	100	1	0 1 0 0			
		FA	100	2	75 30 42 36			
Spontaneous tumor pct: 6%	in ctrl. - Total			-	6 2 0 1			

Analysis #6 (Female Rats): All sarcoma (000400) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
For All Tissues	(LMPST	) FA	73	1	1 0 0 0	0.835	0.802	0.959
Sarcoma	(S	) FA	73	2	97 46 46 46			
		FA	74	1	1 0 0 0			
		FA	74	2	96 46 45 46			
		FA	96	1	0 0 1 0			
		FA	96	2	72 39 36 39			
Spontaneous tumor pct: 2%	in ctrl. - Total			-	2 0 1 0			

Analysis #7 (Male):

Skin (000510):

- squamous cell carcinoma (000143) + papilloma (000300) + Carcinoma (000140)
- lipoma (000240) + fibrolipoma (000241)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Skin	(SK	) IN	53-78	1	1 0 0 0	0.705	0.681	0.799
Squamous Cell Carcinoma+	(SPC	) IN	53-78	2	4 6 2 2			
Papilloma+Carcinoma		IN	92-104	1	1 0 0 1			
		IN	92-104	2	11 10 4 8			
		IN	105-106	1	6 3 5 0			
		IN	105-106	2	62 25 35 35			
		FA	86	1	0 0 0 1			
		FA	86	2	87 41 47 47			
		FA	96	1	0 0 1 0			
		FA	96	2	77 36 43 39			
Spontaneous tumor pct: 8%	in ctrl. - Total			-	8 3 6 2			
Skin	(SKI	) IN	105-106	1	0 1 0 2	0.090	0.054	0.241
Lipoma+fibrolipoma	(LF	) IN	105-106	2	68 27 40 33			
Spontaneous tumor pct: <= 1%	in ctrl. - Total			-	0 1 0 2			

Mammary Gland (000320):

- **Carcinoma (000140)+Adenocarcinoma (000141)+Squamous cell carcinoma (000143)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Mammarygland	(MAM)	IN	105-106	1	1 1 2 0	0.481	0.424	0.722
Carcinoma+Adenocarcinoma+ Squamous Cell Carcinoma	(CAS)	IN	105-106	2	67 27 38 35			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		-	1 1 2 0			

Liver (000280):

- **Hepatocellular Adenoma (000103) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Liver	(LIV)	IN	92-104	1	2 0 0 0	0.991	0.985	0.997
Adenoma(hepatocellular)+	(HC)	IN	92-104	2	10 10 5 9			
Carcinoma		IN	105-106	1	4 0 0 1			
		IN	105-106	2	64 28 40 34			
Spontaneous tumor pct: 6% in ctrl. - Total		-		-	6 0 0 1			

Pituitary (000410):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Pituitary	(PIT)	IN	53-78	1	2 0 0 1	0.641	0.628	0.689
Adenoma+Carcinoma	(ADECAR)	IN	53-78	2	1 3 0 1			
		IN	79-91	1	2 1 2 1			
		IN	79-91	2	3 0 0 0			
		IN	92-104	1	4 5 0 3			
		IN	92-104	2	3 1 1 1			
		IN	105-106	1	47 20 27 20			
		IN	105-106	2	21 8 13 15			
		FA	64	1	0 0 1 0			
		FA	64	2	97 50 48 50			
		FA	65	1	0 1 0 0			
		FA	65	2	96 49 48 49			
		FA	68	1	0 1 0 0			
		FA	68	2	96 47 48 49			
		FA	71	1	1 0 0 0			
		FA	71	2	94 46 48 49			
		FA	72	1	1 0 1 0			
		FA	72	2	93 46 47 49			
		FA	74	1	0 1 0 0			
		FA	74	2	92 45 47 49			
		FA	80	1	0 1 0 0			
		FA	80	2	89 43 47 48			
		FA	81	1	1 2 0 0			
		FA	81	2	88 41 47 48			
		FA	83	1	1 0 0 0			
		FA	83	2	87 41 47 48			
		FA	86	1	0 1 0 0			
		FA	86	2	87 40 47 48			

	FA 87	1	0	0	0	1
	FA 87	2	86	40	47	46
	FA 88	1	0	0	0	1
	FA 88	2	86	40	47	45
	FA 90	1	1	1	0	0
	FA 90	2	84	38	45	45
	FA 91	1	4	0	0	1
	FA 91	2	80	38	45	44
	FA 92	1	0	1	0	1
	FA 92	2	80	37	45	43
	FA 93	1	0	0	1	0
	FA 93	2	79	36	44	42
	FA 94	1	0	0	0	1
	FA 94	2	78	36	44	40
	FA 95	1	1	0	0	0
	FA 95	2	77	36	44	40
	FA 96	1	0	0	0	1
	FA 96	2	77	36	44	38
	FA 97	1	0	0	1	1
	FA 97	2	77	36	42	37
	FA 98	1	0	1	0	1
	FA 98	2	75	35	42	36
	FA 99	1	0	1	0	0
	FA 99	2	75	33	42	36
	FA 100	1	1	0	1	0
	FA 100	2	74	31	41	36
	FA 101	1	0	1	0	0
	FA 101	2	74	29	41	36
	FA 102	1	1	0	0	0
	FA 102	2	71	29	41	35
	FA 103	1	2	0	1	0
	FA 103	2	69	28	40	35
Spontaneous tumor pct: 69%	in ctrl. - Total	-	69	38	35	33

Thyroid (000610):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Thyroids	(THY)	IN	79-91	1	1	0	0	0	0.821	0.802	0.889
Adenoma+Carcinoma	(ACARC)	IN	79-91	2	11	6	2	4			
		IN	92-104	1	0	1	0	0			
		IN	92-104	2	12	8	5	9			
		IN	105-106	1	9	1	1	5			
		IN	105-106	2	59	27	39	30			
		FA	99	1	0	1	0	0			
		FA	99	2	75	33	42	36			
Spontaneous tumor pct: 10%	in ctrl. - Total			-	10	3	1	5			

Adrenal (000100):

- **Adenoma (000100) + Carcinoma (000140)**
- **Phaeochromocytoma (000310)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP /CONT CORR =P(STAT.GE.OBSERVED)
Adrenals	(ADR)	IN	79-91	1	0 0 1 0	0.608	0.587	0.690
Adenoma+Carcinoma	(AC)	IN	79-91	2	12 6 1 4			
		IN	92-104	1	0 0 1 1			
		IN	92-104	2	12 9 4 8			
		IN	105-106	1	15 7 6 6			
		IN	105-106	2	53 21 34 29			
		FA	99	1	0 1 0 0			
		FA	99	2	75 33 42 36			
Spontaneous tumor pct: 15% in ctrl. - Total				-	15 8 8 7			
Adrenals	(AD)	IN	105-106	1	1 0 0 0	1.000	0.873	0.996
Phaeochromocytoma	(P)	IN	105-106	2	67 28 40 35			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			

Parathyroids (000390):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP /CONT CORR =P(STAT.GE.OBSERVED)
Parathyroids	(PAR)	IN	53-78	1	1 0 0 0	0.318	0.270	0.517
Adenoma+Carcinoma	(ADCR)	IN	53-78	2	4 6 2 2			
		IN	79-91	1	0 0 1 0			
		IN	79-91	2	12 6 1 4			
		IN	92-104	1	0 0 1 0			
		IN	92-104	2	12 10 4 9			
		IN	105-106	1	0 2 1 0			
		IN	105-106	2	68 26 39 35			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 2 3 0			

Prostate (000430):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP /CONT CORR =P(STAT.GE.OBSERVED)
Prostate	(PROS)	IN	79-91	1	1 0 0 0	0.694	0.633	0.870
Adenoma+Carcinoma	(ADC)	IN	79-91	2	11 6 2 4			
		IN	92-104	1	0 1 0 0			
		IN	92-104	2	12 9 5 9			
		IN	105-106	1	1 0 0 1			
		IN	105-106	2	67 28 40 34			
Spontaneous tumor pct: 2% in ctrl. - Total				-	2 1 0 1			

Brain (000130):

- **Glioma (000190) + Ependymoma (000160)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
Brain	(BR	) IN	105-106	1	1 1 0 0	0.937	0.896	0.984
Glioma+Ependymoma	(GLIEP	) IN	105-106	2	67 27 40 35			
		FA	72	1	1 0 0 0			
		FA	72	2	93 46 48 49			
Spontaneous tumor pct: 2%		in ctrl. -	Total	-	2 1 0 0			

Lung (000290):

- **adenoma (000100) + adenocarcinoma (000141)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
Lungs	(LUN	) IN	79-91	1	1 0 0 0	1.000	0.987	0.998
Adenoma+adenocarcinoma	(AA	) IN	79-91	2	11 6 2 4			
		IN	92-104	1	1 0 0 0			
		IN	92-104	2	11 10 5 9			
		IN	105-106	1	2 0 0 0			
		IN	105-106	2	66 28 40 35			
Spontaneous tumor pct: 4%		in ctrl. -	Total	-	4 0 0 0			

Salivary gland (000480):

- **squamous cell carcinoma (000143) + carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
Salivarygland	(SG	) IN	105-106	1	1 0 0 0	1.000	0.873	0.996
Squamous Cell Carcinoma+ Carcinoma	(SC	) IN	105-106	2	67 28 40 35			
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	1 0 0 0			

Pancreas (000380):

- **insuloma (000220) + adenoma (000100)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
Pancreas	(PAN	) IN	53-78	1	0 1 0 0	0.836	0.822	0.888
Insuloma+Adenoma	(IA	) IN	53-78	2	5 5 2 2			
		IN	79-91	1	2 1 0 0			
		IN	79-91	2	10 5 2 4			
		IN	92-104	1	2 1 0 0			
		IN	92-104	2	10 9 5 9			
		IN	105-106	1	10 6 6 4			
		IN	105-106	2	58 22 34 31			
Spontaneous tumor pct: 14%		in ctrl. -	Total	-	11 9 6 4			

Testicles (000560) + Epididymides (000160):

- **interstitial cell tumor (001003)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
Testicles+Epididymides	(ET	)	IN 92-104	1	0 0 0 1	0.956	0.947	0.980
Tumour(interstitialcell	(ICT	)	IN 92-104	2	12 10 5 8			
			IN 105-106	1	8 1 3 0			
			IN 105-106	2	60 27 37 35			
Spontaneous tumor pct: 8%	in ctrl. -		Total	-	8 1 3 1			

Analysis #7 (Female):

Skin (000510):

- **squamous cell carcinoma (000143) + papilloma (000300) + Carcinoma (000140)**
- **lipoma (000240) + fibrolipoma (000241)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
Skin	(SK	)	IN 92-104	1	0 1 0 0	0.920	0.907	0.960
Squamous Cell Carcinoma+	(SPC	)	IN 92-104	2	14 4 5 6			
Papilloma+Carcinoma			IN 105-106	1	5 0 2 0			
			IN 105-106	2	59 34 29 35			
			FA 86	1	1 0 0 0			
			FA 86	2	84 43 42 43			
			FA 87	1	0 0 1 0			
			FA 87	2	83 43 40 42			
			FA 88	1	1 0 0 0			
			FA 88	2	82 43 40 41			
			FA 98	1	0 0 1 0			
			FA 98	2	70 39 35 39			
			FA 99	1	0 1 0 0			
			FA 99	2	70 38 35 39			
Spontaneous tumor pct: 7%	in ctrl. -		Total	-	7 2 4 0			
Skin	(SKI	)	IN 79-91	1	1 0 0 0	0.920	0.866	0.979
Lipoma+Fibrolipoma	(LF	)	IN 79-91	2	12 6 7 2			
			IN 92-104	1	0 1 0 0			
			IN 92-104	2	14 5 6 6			
			IN 105-106	1	1 0 0 0			
			IN 105-106	2	63 34 31 35			
Spontaneous tumor pct: 2%	in ctrl. -		Total	-	2 1 0 0			

Mammary Gland (000320):

- **Adenoma (000100) + Fibroadenoma (000102) + adenofibroma (000171)**
- **Carcinoma (000140)+Adenocarcinoma (000141)+Squamous cell carcinoma (000143)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT .GE. OBSERVED)
Mammarygland	(MG	)	IN 53-78	1	0 0 0 1	0.762	0.740	0.845
Adenoma+Fibroadenoma+	(AFA	)	IN 53-78	2	8 4 5 3			
Adenofibroma			IN 92-104	1	3 0 0 2			
			IN 92-104	2	10 6 6 4			

		IN 105-106	1	6	2	1	1			
		IN 105-106	2	58	32	30	34			
		FA 74	1	0	0	0	1			
		FA 74	2	97	46	45	45			
		FA 90	1	0	0	1	0			
		FA 90	2	78	42	38	41			
		FA 100	1	1	0	0	0			
		FA 100	2	68	37	35	39			
Spontaneous tumor pct: 10%	in ctrl.	- Total	-	10	2	2	5			
Mammarygland	(MAM	) IN 105-106	1	10	6	3	2	0.840	0.826	0.892
Carcinoma+Adenocarcinoma+	(CAS	) IN 105-106	2	54	28	28	33			
Squamous Cell Carcinoma		FA 68	1	0	0	1	0			
		FA 68	2	99	47	46	46			
		FA 79	1	0	0	1	0			
		FA 79	2	91	46	43	43			
		FA 88	1	1	0	0	0			
		FA 88	2	82	43	40	41			
		FA 92	1	1	0	0	0			
		FA 92	2	77	40	37	41			
		FA 94	1	0	0	0	1			
		FA 94	2	73	39	37	39			
		FA 102	1	0	0	1	0			
		FA 102	2	66	36	34	36			
		FA 103	1	1	1	1	0			
		FA 103	2	65	35	32	36			
Spontaneous tumor pct: 13%	in ctrl.	- Total	-	13	7	7	3			

Liver (000280):

- **Hepatocellular Adenoma (000103) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Liver	(LIV	) IN	79-91	1	0	0	0	1	0.312	0.264	0.507
Adenoma(hepatocellular)+	(HAC	) IN	79-91	2	12	6	7	1			
Carcinoma		IN	105-106	1	0	1	1	1			
		IN	105-106	2	64	33	30	34			
		FA	74	1	1	0	0	0			
		FA	74	2	96	46	45	46			
		FA	88	1	1	0	0	0			
		FA	88	2	82	43	40	41			
Spontaneous tumor pct: 2%	in ctrl.	- Total		-	2	1	1	2			

Pituitary (000410):

- **Adenoma (000100) + Carcinoma (000140)**
- **Phaeochromocytoma (000310)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Pituitary	(PIT	) IN	0-52	1	0	0	0	1	0.968	0.965	0.976
Adenoma+Carcinoma	(ADC	) IN	0-52	2	0	0	1	1			
		IN	53-78	1	1	1	1	0			
		IN	53-78	2	2	0	1	1			
		IN	79-91	1	2	0	3	0			
		IN	79-91	2	1	1	0	1			
		IN	92-104	1	2	2	1	1			

IN 92-104	2	1	1	2	0
IN 105-106	1	54	29	25	25
IN 105-106	2	9	5	6	10
FA 47	1	1	0	0	0
FA 47	2	99	50	50	49
FA 56	1	0	0	1	0
FA 56	2	99	50	48	48
FA 57	1	0	1	0	0
FA 57	2	99	49	48	48
FA 58	1	0	1	0	0
FA 58	2	99	48	48	48
FA 66	1	0	0	0	2
FA 66	2	99	47	47	46
FA 70	1	1	1	0	0
FA 70	2	98	46	46	46
FA 73	1	0	0	1	0
FA 73	2	98	46	45	46
FA 74	1	1	0	0	0
FA 74	2	96	46	45	46
FA 75	1	1	0	0	1
FA 75	2	95	46	45	44
FA 76	1	0	0	0	1
FA 76	2	95	46	45	43
FA 77	1	2	0	1	0
FA 77	2	92	46	44	43
FA 79	1	1	0	2	0
FA 79	2	90	46	42	43
FA 80	1	1	1	0	0
FA 80	2	89	45	42	43
FA 81	1	0	1	0	0
FA 81	2	89	43	42	43
FA 82	1	1	0	0	0
FA 82	2	88	43	42	43
FA 83	1	2	0	0	0
FA 83	2	86	43	42	43
FA 84	1	1	0	0	0
FA 84	2	85	43	42	43
FA 86	1	1	0	0	0
FA 86	2	84	43	42	43
FA 87	1	0	0	1	1
FA 87	2	83	43	40	41
FA 88	1	2	0	0	0
FA 88	2	81	43	40	41
FA 89	1	1	1	1	0
FA 89	2	78	42	39	41
FA 91	1	0	2	0	0
FA 91	2	78	40	38	41
FA 92	1	4	1	0	0
FA 92	2	74	39	37	41
FA 94	1	0	0	0	1
FA 94	2	73	39	37	39
FA 96	1	1	0	0	0
FA 96	2	71	39	37	39
FA 97	1	1	0	0	0
FA 97	2	70	39	36	39
FA 98	1	0	0	1	0
FA 98	2	70	39	35	39

		FA 99	1	1	2	0	0
		FA 99	2	69	37	35	39
		FA 100	1	1	0	0	3
		FA 100	2	68	37	35	36
		FA 101	1	1	0	0	0
		FA 101	2	66	37	35	36
		FA 102	1	0	0	2	0
		FA 102	2	66	36	33	36
		FA 103	1	1	0	0	0
		FA 103	2	65	36	33	36
		FA 104	1	1	0	0	1
		FA 104	2	64	34	32	35
		FA 106	1	1	0	0	0
		FA 106	2	26	13	11	13
Spontaneous tumor pct: 87%	in ctrl. -	Total	-	87	43	40	37

Thyroid (000610):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Thyroids	(THY)	IN	79-91	1	1	0	0	0	0.634	0.597	0.782
Adenoma+Carcinoma	(AC)	IN	79-91	2	12	6	7	2			
		IN	105-106	1	3	2	1	2			
		IN	105-106	2	61	32	30	33			
Spontaneous tumor pct: 4%	in ctrl. -	Total	-		4	2	1	2			

Adrenal (000100):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Adrenals	(ADR)	IN	79-91	1	1	0	0	0	0.851	0.834	0.911
Adenoma+Carcinoma	(ADCAR)	IN	79-91	2	12	6	7	2			
		IN	92-104	1	0	0	1	1			
		IN	92-104	2	14	5	5	5			
		IN	105-106	1	8	2	3	1			
		IN	105-106	2	56	32	28	34			
		FA	99	1	0	1	0	0			
		FA	99	2	70	38	35	39			
Spontaneous tumor pct: 9%	in ctrl. -	Total	-		9	3	4	2			

Parathyroids (000390):

- **Adenoma (000100)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Parathyroids	(PAR)	IN	92-104	1	0	1	0	0	0.304	0.257	0.673
Adenoma	(A)	IN	92-104	2	14	5	6	6			
		IN	105-106	1	0	0	1	0			
		IN	105-106	2	64	34	30	35			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total	-		0	1	1	0			

Brain (000130):

- **Glioma (000190) + Ependymoma (000160)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Brain	(BR)	IN	105-106	1	0 1 0 0	0.526	0.432	0.824
Glioma+Ependymoma	(GLIEP)	IN	105-106	2	64 33 31 35			
		FA	57	1	0 1 0 0			
		FA	57	2	99 49 48 48			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 2 0 0			

Lung (000290):

- **adenoma (000100) + adenocarcinoma (000141)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Lungs	(LUN)	IN	53-78	1	1 0 0 0	1.000	0.887	0.997
Adenoma+Adenocarcinoma	(AAC)	IN	53-78	2	7 4 5 5			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			

Salivary gland (000480):

- **squamous cell carcinoma (000143) + carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Salivarygland	(SG)	IN	105-106	1	1 0 0 0	1.000	0.873	0.996
Squamous Cell Carcinoma+ Carcinoma	(SCCC)	IN	105-106	2	63 34 31 35			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			

Pancreas (000380):

- **insuloma (000220) + adenoma (000100)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Pancreas	(PAN)	IN	92-104	1	0 0 0 1	0.502	0.468	0.638
Insuloma+Adenoma	(IA)	IN	92-104	2	14 6 6 5			
		IN	105-106	1	5 4 2 2			
		IN	105-106	2	59 30 29 33			
Spontaneous tumor pct: 5% in ctrl. - Total				-	5 4 2 3			

Uterus (000650):

- **Carcinoma (000140)+Adenocarcinoma (000141)+Squamous cell carcinoma (000143)**
- **Fibroadenoma (000102) + adenofibroma (000171)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Uterus	(UT)	IN	105-106	1	0 0 1 0	0.844	0.813	0.963
Carcinoma+Adenocarcinoma+ Squamous Cell Carcinoma	(CASCC)	IN	105-106	2	64 34 30 35			
		FA	88	1	1 0 0 0			
		FA	88	2	82 43 40 41			
		FA	101	1	1 0 0 0			
		FA	101	2	66 37 35 36			

Spontaneous tumor pct: 2%	in ctrl. - Total	-		2	0	1	0					
Uterus	(UTER)	IN	53-78	1	1	0	0	0	1.000	0.952	0.997	
Adenoma(fibro-)+	(FAF)	IN	53-78	2	7	4	5	5				
Adenofibroma		IN	105-106	1	1	0	0	0				
		IN	105-106	2	63	34	31	35				
Spontaneous tumor pct: 2%	in ctrl.											

Analysis #8 (Male):

Pituitary (000410) + Thyroid (000610) + Adrenal (000100) + Parathyroids (000390):

- **Adenoma (000100) + Carcinoma (000140)**
- **Phaeochromocytoma (000310)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Combination	(COMB)	IN	53-78	1	2	0	0	1	0.880	0.873	0.906
Adenoma+Carcinoma	(AC)	IN	53-78	2	1	3	0	1			
		IN	79-91	1	2	1	2	1			
		IN	79-91	2	3	0	0	0			
		IN	92-104	1	4	4	1	3			
		IN	92-104	2	3	0	0	1			
		IN	105-106	1	57	24	29	21			
		IN	105-106	2	11	4	11	14			
		FA	64	1	0	0	1	0			
		FA	64	2	97	50	48	50			
		FA	65	1	0	1	0	0			
		FA	65	2	96	49	48	49			
		FA	68	1	0	1	0	0			
		FA	68	2	96	47	48	49			
		FA	71	1	1	0	0	0			
		FA	71	2	94	46	48	49			
		FA	72	1	1	0	1	0			
		FA	72	2	93	46	47	49			
		FA	74	1	0	1	0	0			
		FA	74	2	92	45	47	49			
		FA	80	1	0	1	0	0			
		FA	80	2	89	43	47	48			
		FA	81	1	1	2	0	0			
		FA	81	2	88	41	47	48			
		FA	83	1	1	0	0	0			
		FA	83	2	87	41	47	48			
		FA	86	1	0	1	0	0			
		FA	86	2	87	40	47	48			
		FA	87	1	0	0	0	1			
		FA	87	2	86	40	47	46			
		FA	88	1	0	0	0	1			
		FA	88	2	86	40	47	45			
		FA	90	1	1	1	0	0			
		FA	90	2	84	38	45	45			
		FA	91	1	4	0	0	1			
		FA	91	2	80	38	45	44			
		FA	92	1	0	1	0	1			
		FA	92	2	80	37	45	43			

			FA 93	1	0	0	1	0		
			FA 93	2	79	36	44	42		
			FA 94	1	0	0	0	1		
			FA 94	2	78	36	44	40		
			FA 95	1	1	0	0	0		
			FA 95	2	77	36	44	40		
			FA 96	1	0	0	0	1		
			FA 96	2	77	36	44	38		
			FA 97	1	0	0	1	1		
			FA 97	2	77	36	42	37		
			FA 98	1	0	1	0	1		
			FA 98	2	75	35	42	36		
			FA 99	1	0	3	0	0		
			FA 99	2	75	31	42	36		
			FA 100	1	1	0	1	0		
			FA 100	2	74	31	41	36		
			FA 101	1	0	1	0	0		
			FA 101	2	74	29	41	36		
			FA 102	1	1	0	0	0		
			FA 102	2	71	29	41	35		
			FA 103	1	2	0	1	0		
			FA 103	2	69	28	40	35		
Spontaneous tumor pct: 79%		in ctrl. -	Total	-	79	43	38	34		
Combination	(COMBN)	IN	105-106	1	1	0	0	0	1.000	0.873 0.996
Phaeochromocytoma	(P)	IN	105-106	2	67	28	40	35		
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-						

Analysis #8 (Female):
Pituitary (000410) + Thyroid (000610) + Adrenal (000100) + Parathyroids (000390): - Adenoma (000100) + Carcinoma (000140)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB =P(STAT .GE. OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Combination	(comb)	IN	0-52	1	0	0	0	1	0.975	0.973	0.982
Adenoma+Carcinoma	(ac)	IN	0-52	2	0	0	1	1			
		IN	53-78	1	1	1	1	0			
		IN	53-78	2	2	0	1	1			
		IN	79-91	1	2	0	3	0			
		IN	79-91	2	1	1	0	1			
		IN	92-104	1	2	2	1	1			
		IN	92-104	2	1	1	2	0			
		IN	105-106	1	56	30	25	26			
		IN	105-106	2	7	4	6	9			
		FA	47	1	1	0	0	0			
		FA	47	2	99	50	50	49			
		FA	56	1	0	0	1	0			
		FA	56	2	99	50	48	48			
		FA	57	1	0	1	0	0			
		FA	57	2	99	49	48	48			
		FA	58	1	0	1	0	0			
		FA	58	2	99	48	48	48			
		FA	66	1	0	0	0	2			
		FA	66	2	99	47	47	46			
		FA	70	1	1	1	0	0			
		FA	70	2	98	46	46	46			
		FA	73	1	0	0	1	0			

FA 73	2	98	46	45	46
FA 74	1	1	0	0	0
FA 74	2	96	46	45	46
FA 75	1	1	0	0	1
FA 75	2	95	46	45	44
FA 76	1	0	0	0	1
FA 76	2	95	46	45	43
FA 77	1	2	0	1	0
FA 77	2	92	46	44	43
FA 79	1	1	0	2	0
FA 79	2	90	46	42	43
FA 80	1	1	1	0	0
FA 80	2	89	45	42	43
FA 81	1	0	1	0	0
FA 81	2	89	43	42	43
FA 82	1	1	0	0	0
FA 82	2	88	43	42	43
FA 83	1	2	0	0	0
FA 83	2	86	43	42	43
FA 84	1	1	0	0	0
FA 84	2	85	43	42	43
FA 86	1	1	0	0	0
FA 86	2	84	43	42	43
FA 87	1	0	0	1	1
FA 87	2	83	43	40	41
FA 88	1	2	0	0	0
FA 88	2	81	43	40	41
FA 89	1	1	1	1	0
FA 89	2	78	42	39	41
FA 91	1	0	2	0	0
FA 91	2	78	40	38	41
FA 92	1	4	1	0	0
FA 92	2	74	39	37	41
FA 94	1	0	0	0	1
FA 94	2	73	39	37	39
FA 96	1	1	0	0	0
FA 96	2	71	39	37	39
FA 97	1	1	0	0	0
FA 97	2	70	39	36	39
FA 98	1	0	0	1	0
FA 98	2	70	39	35	39
FA 99	1	1	2	0	0
FA 99	2	69	37	35	39
FA 100	1	1	0	0	3
FA 100	2	68	37	35	36
FA 101	1	1	0	0	0
FA 101	2	66	37	35	36
FA 102	1	0	0	2	0
FA 102	2	66	36	33	36
FA 103	1	1	0	0	0
FA 103	2	65	36	33	36
FA 104	1	1	0	0	1
FA 104	2	64	34	32	35
FA 106	1	1	0	0	0
FA 106	2	26	13	11	13
Spontaneous tumor pct: 89% in ctrl. - Total	-	89	44		

IIe. Summary of Rat Study (Study No. 3805/86)

For the male as well as female rats, no statistically significant positive linear trend or increased mortality was detected in the treated groups when compared with the control.

None of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups when compared with the control.

From the survival criteria, it can be concluded that enough numbers of rats were exposed to the drug for a sufficient amount of time in both sexes. From the weight gain criteria, it can be concluded that the high dose used (0.8 mg/kg/day) may be close to the maximum tolerated dose for both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

Additional analyses (as requested by the Reviewing Pharmacologist) for the male as well as female rats showed no statistically significant dose-tumor positive linear trend in the treated groups when compared with the control.

APPEARS THIS WAY
ON ORIGINAL

III. THE MOUSE STUDY (Study No. 4184/87)

IIIa. Design

A 104-week study was conducted in mice to investigate the carcinogenic potential of MOBIC® (meloxicam) when administered orally. Three groups of 50 male and 50 female mice [redacted](SPF)) were treated with MOBIC® (meloxicam) in concentrations of 2.0 (low), 4.0 (medium) and 8.0 (high) mg/kg/day; and, one control group of 100 male and 100 female mice [redacted](SPF)) received the standardized diet without dosing. For the female mice, the study was terminated after 99 weeks because of high mortality (between 73% and 82%). Please note that the high dose group had a total of 100 animals with 51 being male and 49 being female mice.

IIIb. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the papers by [redacted](1972) and [redacted](1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics, FDA. The results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold:
(1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and
(2) To determine the significance of a positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al. (1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 6a (male) and 6b (female) summarize the number of animals died at different time-intervals. Note that the high dose group had a total of 100 animals with 51 being male and 49 being female mice. Tables 7a and 7b summarize the intercurrent mortality data for the male and female mice respectively. For the male mice, there appears to be an increased mortality in the medium dose group as compared to other dose groups. For the female mice, the study was terminated after 99 weeks because of high mortality (between 73% for high-dose group and 82% for medium-dose group).

- Figures 2a and 2b depict the [redacted]survival distributions for males and females respectively. For the male mice, after 60 weeks, there appears to be an increased mortality in the medium dose group when compared to the other doses. For the female mice, the curves for different dose groups intertwine each other

suggesting that there is no significant difference between their survival patterns. The test of homogeneity yields non-significant results for the male mice as well as for the female mice (Tables 8a and 8b in the Appendix).

- Tables 8a and 8b display the p-values of the test of homogeneity and of positive linear trends for males and females, respectively, using the [redacted] test and the generalized [redacted] test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the test which gives equal weight to all deaths.

  The test of homogeneity and the test of linear trend yield non-significant results for the male mice as well as for the female mice.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of a positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor types were classified as fatal and non-fatal. Table 9 (Part I) displays selected organs and organ codes. Table 9 (Part II) displays tumors and tumor codes.

Following Peto et al. (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused death for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 2, 4, and 8 for the control, low, medium, and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 2.0, 4.0, and 8.0 mg/kg/day of MOBIC® (meloxicam). The time-intervals used were 0-52, 53-78, 79-91, 92-104, 105 and beyond for males; and 0-52, 53-78, 79-91, 92-99, 100 and beyond for females.

The tumor analysis results are displayed in the Appendix. Tables 10a and 10b describe the p-values for the test of trend based on the tumor data for males and females, respectively. The rule proposed by Haseman (1983) could be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by Lin and Rahman (1995) for trend tests was used in this review. This rule for trend tests says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of 1% or less (rare tumors) should be tested at a 0.025 significance level, otherwise (for common tumors) a 0.005 significance level should be used.

On the basis of the rule for trend tests described above, no statistically significant positive linear trend or increased incidence was detected in any of the tested tumor types for the male mice. But, for the female mice, the following significant linear dose tumor-trends were indicated.

The number of females with adenoma (hepatocellular) for the liver for various dose groups is described below (from Table 10b).

Female Mice			Tumor Rate				Trend Test
Organ	Tumor Name	Tumor Type	Control N=100	Low N=50	Medium N=50	High N=49	p-value
Liver	Adenoma (Hepatocellular)	Incidental	0	1	0	3	0.0148

IIIc. Additional Analyses Requested by the Reviewing Pharmacologist

The reviewing pharmacologist requested the following 6 analyses for combined organs and combined tumors for males and females.

Analysis #1: All heamangioma (000200) together **for all tissues**

Analysis #2: All heamangioma (000200) + angioma (000130) + angiosarcoma (000401) together **for all tissues**

Analysis #3: All lymphoma (000270) together **for all tissues**

Analysis #4: All sarcoma (000400) together **for all tissues**

Analysis #5: Skin (000510):

- squamous cell carcinoma (000143) + papilloma (000300)

Stomach (000550) + Intestine (000220):

- Squamous cell carcinoma (000143) + Papilloma (000300)
- Polyp (000320)

Liver (000280):

- Hepatocellular Adenoma (000103) + Carcinoma (000142)

Pituitary (000410):

- Adenoma (000100) + Carcinoma (000140)

Thyroid (000610):

- Adenoma (000100) + Carcinoma (000140)

Adrenal (000100):

- Adenoma (000100) + Carcinoma (000140)

Parathyroids (000390):

- Adenoma (000100) + Carcinoma (000140)

Brain (000130) + Spinal cord (000520):
- Glioma (000190) + Ependymoma (000160)

Uterus (000650):
- sarcoma (000400) + myoma (000280) + leimyosarcoma(000404)

Seminal vesicle (000490) + Preputial gland (000420):
- Adenoma (000100) + Carcinoma (000140)

Lung (000290):
- adenoma (000100) + carcinoma (000140) + adenocarcinoma (000141)

Pancreas (000380):
- insuloma (000220) + carcinoma (000140)

Analysis #6: Pituitary (000410) + Thyroid (000610) + Adrenal (000100) + Parathyroids (000390):
- Adenoma (000100) + Carcinoma (000140)

These analyses were performed on the available data. Results are given below. No statistically significant dose-tumor positive linear trend was detected.

Analysis #1 (Male): All heamangioma (000200) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
For All Tissues	(LSSU)	IN	53-78	1	0 0 0 1	0.373	0.343	0.364
Haemangioma	(H)	IN	53-78	2	17 6 9 5			
		IN	79-91	1	0 0 0 1			
		IN	79-91	2	15 6 12 7			
		IN	105-105	1	2 1 1 0			
		IN	105-105	2	38 22 14 19			
		FA	79	1	0 0 1 0			
		FA	79	2	82 41 35 40			
		FA	84	1	1 0 0 0			
		FA	84	2	76 37 31 38			
		FA	93	1	0 1 0 0			
		FA	93	2	62 34 22 32			
Spontaneous tumor pct: 3%	in ctrl. -	Total		-	3 2			

Analysis #1 (Female): All heamangioma (000200) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
For All Tissues	(LSSU)	IN	53-78	1	0 0 1 0	0.388	0.354	0.379
Haemangioma	(H)	IN	53-78	2	25 11 17 17			
		IN	79-91	1	1 0 0 1			
		IN	79-91	2	25 14 13 11			
		IN	92-99	1	1 0 0 0			
		IN	92-99	2	13 8 9 4			
		FA	85	1	0 1 0 0			
		FA	85	2	52 26 26 23			
		FA	92	1	1 0 0 0			
		FA	92	2	39 20 18 18			
		FA	95	1	0 0 0 1			
		FA	95	2	34 17 18 15			
Spontaneous tumor pct: 3%	in ctrl. -	Total		-	3			

Analysis #2 (Male): All heamangioma (000200) + angioma (000130) + angiosarcoma (000401) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
For All Tissues	(FAT)	IN	53-78	1	0 0 0 1	0.407	0.380	0.401
Heamangioma+Angioma+	(HAA)	IN	53-78	2	17 6 9 5			
Angiosarcoma		IN	79-91	1	0 0 0 1			
		IN	79-91	2	15 6 12 7			
		IN	92-104	1	0 1 0 0			
		IN	92-104	2	26 10 8 13			
		IN	105-105	1	2 1 1 0			
		IN	105-105	2	38 22 14 19			
		FA	79	1	0 0 1 0			
		FA	79	2	82 41 35 40			
		FA	84	1	1 0 0 0			
		FA	84	2	76 37 31 38			
		FA	93	1	0 1 0 0			
		FA	93	2	62 34 22 32			
Spontaneous tumor pct: 3%	in ctrl. -	Total		-	3 3 2 2			

Analysis #2 (Female): All heamangioma (000200) + angioma (000130) + angiosarcoma (000401) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
For All Tissues	(FAT)	IN	53-78	1	0 0 1 0	0.301	0.270	0.290
Heamangioma+Angioma+	(HAA)	IN	53-78	2	25 11 17 17			
Angiosarcoma		IN	79-91	1	1 0 0 1			
		IN	79-91	2	24 14 13 11			
		IN	92-99	1	1 0 0 0			
		IN	92-99	2	13 8 9 4			
		IN	100-100	1	0 0 0 1			
		IN	100-100	2	25 12 9 12			
		FA	81	1	1 0 0 0			

			FA	81	2	61	32	29	27
			FA	85	1	0	1	0	0
			FA	85	2	52	26	26	23
			FA	92	1	1	0	0	0
			FA	92	2	39	20	18	18
			FA	95	1	0	0	0	1
			FA	95	2	34	17	18	15

Spontaneous tumor pct: 4% in ctrl. - Total

Analysis #3 (Male): All lymphoma (000270) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
For All Tissues	(FAT)	IN	0-52	1	0	0	0	1	0.368	0.357	0.365
Lymphoma	(L)	IN	0-52	2	1	2	4	4			
		IN	53-78	1	1	0	0	0			
		IN	53-78	2	13	4	8	6			
		IN	79-91	1	0	0	2	0			
		IN	79-91	2	11	6	10	5			
		IN	92-104	1	1	0	3	0			
		IN	92-104	2	17	8	4	5			
		IN	105-105	1	9	6	3	2			
		IN	105-105	2	31	17	12	17			
		FA	10	1	0	1	0	0			
		FA	10	2	100	49	57	51			
		FA	49	1	0	0	1	0			
		FA	49	2	99	47	46	47			
		FA	58	1	0	0	1	0			
		FA	58	2	99	47	44	44			
		FA	61	1	0	1	0	0			
		FA	61	2	96	45	41	44			
		FA	67	1	1	1	0	0			
		FA	67	2	94	43	40	43			
		FA	73	1	1	0	0	0			
		FA	73	2	87	42	37	41			
		FA	77	1	1	0	0	0			
		FA	77	2	84	41	37	41			
		FA	79	1	1	0	0	0			
		FA	79	2	81	41	36	40			
		FA	80	1	1	0	0	0			
		FA	80	2	80	40	35	39			
		FA	82	1	0	0	1	0			
		FA	82	2	78	38	33	38			
		FA	84	1	1	0	0	0			
		FA	84	2	76	37	31	38			
		FA	86	1	2	0	0	1			
		FA	86	2	72	36	28	36			
		FA	87	1	0	0	0	1			
		FA	87	2	70	36	28	35			
		FA	89	1	0	0	0	1			
		FA	89	2	67	36	28	34			
		FA	92	1	2	0	0	0			
		FA	92	2	64	35	23	32			
		FA	93	1	0	0	0	1			
		FA	93	2	62	35	22	31			
		FA	95	1	0	0	0	2			

				FA	95	2	62	32	18	29
				FA	96	1	0	0	0	1
				FA	96	2	60	31	18	28
				FA	97	1	1	0	0	0
				FA	97	2	58	31	18	28
				FA	98	1	1	1	0	1
				FA	98	2	57	29	18	26
				FA	99	1	0	1	0	1
				FA	99	2	57	27	18	24
				FA	100	1	1	1	0	0
				FA	100	2	54	26	18	24
				FA	101	1	1	0	1	0
				FA	101	2	49	26	17	22
				FA	102	1	2	0	0	0
				FA	102	2	45	26	16	22
				FA	103	1	0	1	0	1
				FA	103	2	44	25	16	21
				FA	104	1	0	0	0	1
				FA	104	2	42	25	15	19
Spontaneous tumor pct: 27%			in ctrl. -	Total		-	27	13	12	

Analysis #3 (Female): All lymphoma (000270) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Adrenals	(FAT)	IN	53-78	1	1	1	0	0	0.753	0.745	0.750
Lymphoma	(L)	IN	53-78	2	11	7	11	12			
		IN	79-91	1	1	0	1	0			
		IN	79-91	2	9	12	5	5			
		IN	92-99	1	3	2	3	0			
		IN	92-99	2	5	3	3	3			
		IN	100-100	1	14	10	3	8			
		IN	100-100	2	11	2	8	5			
		FA	58	1	1	1	0	0			
		FA	58	2	89	45	44	44			
		FA	59	1	2	0	0	1			
		FA	59	2	87	44	44	42			
		FA	61	1	0	0	2	0			
		FA	61	2	86	44	41	42			
		FA	62	1	0	0	0	1			
		FA	62	2	86	44	40	41			
		FA	66	1	0	1	0	0			
		FA	66	2	84	41	40	41			
		FA	67	1	1	0	1	0			
		FA	67	2	83	41	39	40			
		FA	68	1	1	0	0	0			
		FA	68	2	82	41	39	40			
		FA	69	1	2	0	1	0			
		FA	69	2	79	41	37	40			
		FA	70	1	1	0	1	0			
		FA	70	2	76	41	36	40			
		FA	72	1	0	0	1	2			
		FA	72	2	75	41	35	35			
		FA	74	1	1	1	0	0			
		FA	74	2	73	39	34	33			
		FA	75	1	2	0	0	0			

FA 75	2	71	38	34	33
FA 76	1	0	0	0	1
FA 76	2	70	38	34	32
FA 77	1	0	0	1	0
FA 77	2	70	38	32	31
FA 78	1	2	0	0	0
FA 78	2	66	37	32	31
FA 79	1	2	0	0	0
FA 79	2	64	35	31	30
FA 80	1	2	0	1	0
FA 80	2	62	34	29	28
FA 81	1	3	0	1	1
FA 81	2	59	32	28	26
FA 83	1	2	0	0	0
FA 83	2	54	30	27	26
FA 84	1	0	0	1	2
FA 84	2	52	30	26	24
FA 85	1	0	1	0	0
FA 85	2	52	26	26	23
FA 86	1	2	0	1	1
FA 86	2	50	24	25	21
FA 87	1	1	1	1	2
FA 87	2	49	22	24	19
FA 88	1	2	0	2	0
FA 88	2	47	22	21	19
FA 89	1	1	0	0	1
FA 89	2	46	22	21	18
FA 90	1	1	1	0	0
FA 90	2	44	21	20	18
FA 92	1	1	1	0	0
FA 92	2	39	19	18	18
FA 93	1	1	0	0	0
FA 93	2	36	19	18	16
FA 94	1	1	0	0	0
FA 94	2	35	17	18	16
FA 95	1	0	1	0	1
FA 95	2	34	16	18	15
FA 96	1	0	0	1	0
FA 96	2	33	15	17	14
FA 97	1	2	0	0	0
FA 97	2	31	14	17	14
FA 98	1	2	0	1	1
FA 98	2	28	14	12	13
FA 99	1	0	1	1	0
FA 99	2	26	13	9	13
Spontaneous tumor pct: 55% in ctrl. - Total		55	22	24	22

Analysis #4 (Male): All sarcoma (000400) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------				EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PRO3	ASYMP PROB /CONT CORR
For All Tissues	(FAT)	IN	92-104	1	0	1	0	0	0.119	0.089	0.100
Sarcoma	(S)	IN	92-104	2	26	10	8	13			
		IN	105-105	1	0	0	0	2			
		IN	105-105	2	40	23	15	17			
		FA	73	1	0	1	0	0			
		FA	73	2	88	41	37	41			

			FA	82	1	0	0	1	0	
			FA	82	2	78	38	33	38	
			FA	100	1	0	1	0	0	
			FA	100	2	55	26	18	24	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	3	1	2	

Analysis #4 (Female): All sarcoma (000400) together for all tissues

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Anus	(FAT)	IN	79-91	1	1	0	0	0	0.662	0.643	0.658
Sarcoma	(S)	IN	79-91	2	23	15	12	12			
		IN	100-100	1	2	2	0	1			
		IN	100-100	2	23	10	9	12			
		FA	50	1	1	0	0	0			
		FA	50	2	92	46	49	47			
		FA	56	1	0	0	0	1			
		FA	56	2	90	46	48	46			
		FA	70	1	1	0	0	0			
		FA	70	2	76	41	37	40			
		FA	81	1	1	0	0	0			
		FA	81	2	61	32	29	27			
		FA	87	1	0	0	1	0			
		FA	87	2	50	23	24	21			
		FA	91	1	1	0	0	0			
		FA	91	2	42	21	19	18			
		FA	92	1	0	0	0	1			
		FA	92	2	40	20	18	17			
		FA	93	1	0	1	0	0			
		FA	93	2	37	18	18	16			
		FA	95	1	0	1	0	0			
		FA	95	2	34	16	18	16			
		FA	97	1	0	0	1	0			
		FA	97	2	33	14	16	14			
		FA	99	1	0	1	0	0			
		FA	99	2	26	13	10	13			
Spontaneous tumor pct: 7% in ctrl. - Total				-	7	5	2	3			

Analysis #5 (Male):

Stomach (000550) + Intestine (000220):
- Polyp (000320)

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Intestine(large)	(STPIN)	IN	105-105	1	1	0	0	0	1.000	0.813	0.855
Polyp	(P)	IN	105-105	2	39	23	15	19			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0			

Liver (000280):

- **Hepatocellular Adenoma (000103) + Carcinoma (000142)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Liver	(LIV)	IN	92-104	1	0 1 0 0	0.675	0.652	0.671
Adenoma(hepatocellular)+	(HAHC)	IN	92-104	2	24 11 8 13			
Carcinoma (hepatocellular)		IN	105-105	1	5 1 0 3			
		IN	105-105	2	35 22 15 16			
		FA	96	1	1 0 0 0			
		FA	96	2	59 31 18 29			
		FA	100	1	1 0 0 0			
		FA	100	2	54 27 18 24			
Spontaneous tumor pct: 7%	in ctrl. - Total		-	-	7 2 0 3			

Pituitary (000410):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Pituitary	(PIT)	IN	105-105	1	1 0 0 0	1.000	0.813	0.855
Adenoma+Carcinoma	(ADC)	IN	105-105	2	39 23 15 19			
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	-	1 0 0 0			

Adrenal (000100):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Adrenals	(ADR)	IN	53-78	1	0 0 0 1	0.254	0.232	0.244
Adenoma+Carcinoma	(ADECAR)	IN	53-78	2	17 6 9 5			
		IN	92-104	1	2 0 0 1			
		IN	92-104	2	24 12 8 12			
		IN	105-105	1	7 4 3 4			
		IN	105-105	2	33 19 12 15			
Spontaneous tumor pct: 9%	in ctrl. - Total		-	-	9 4 3 6			

Brain (000130) + Spinal cord (000520):

- **Glioma (000190) + Ependymoma (000160)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Brain+Spinal Chord	(SCB)	IN	105-105	1	1 0 0 0	1.000	0.813	0.855
Glioma+Ependymoma	(GE)	IN	105-105	2	39 23 15 19			
Spontaneous tumor pct: <= 1%	in ctrl. - Total		-	-	1 0 0 0			

Seminal vesicle (000490) + Preputial gland (000420):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Seminal vesicle	(SVPG)	IN	79-91	1	1 0 0 0	1.000	0.949	0.958
Adenoma + Carcinoma	(ACARCI)	IN	79-91	2	14 6 13 8			

			IN	105-105	1	1	0	0	0
			IN	105-105	2	39	23	15	19
			FA	88	1	1	0	0	0
			FA	88	2	69	36	28	35
Spontaneous tumor pct: 3%		in ctrl. - Total		-		3	0	0	0

Lung (000290):

- **adenoma (000100) + carcinoma (000140) + adenocarcinoma (000141)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------				EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Lungs	(LUN)	IN	0-52	1	0	0	1	0	0.588	0.574	0.584
Adenoma+Carc+Adenocarc	(ACA)	IN	0-52	2	1	3	4	5			
		IN	92-104	1	2	0	0	1			
		IN	92-104	2	20	11	8	10			
		IN	105-105	1	11	5	4	4			
		IN	105-105	2	29	18	11	15			
		FA	66	1	0	0	0	1			
		FA	66	2	95	44	40	43			
		FA	67	1	1	0	0	0			
		FA	67	2	94	44	40	43			
		FA	70	1	0	0	2	0			
		FA	70	2	92	42	38	43			
		FA	73	1	0	1	0	0			
		FA	73	2	88	41	37	41			
		FA	78	1	1	0	0	0			
		FA	78	2	82	41	37	40			
		FA	80	1	1	1	0	0			
		FA	80	2	80	39	35	39			
		FA	82	1	0	0	1	0			
		FA	82	2	78	38	33	38			
		FA	84	1	0	0	1	0			
		FA	84	2	77	37	30	38			
		FA	85	1	1	0	0	0			
		FA	85	2	74	37	29	38			
		FA	87	1	0	0	0	1			
		FA	87	2	70	36	28	35			
		FA	91	1	1	0	0	0			
		FA	91	2	66	35	24	33			
		FA	92	1	2	0	0	0			
		FA	92	2	64	35	23	32			
		FA	93	1	0	0	1	0			
		FA	93	2	62	35	21	32			
		FA	98	1	0	0	0	1			
		FA	98	2	58	30	18	26			
		FA	99	1	0	1	0	1			
		FA	99	2	57	27	18	24			
		FA	101	1	1	0	0	0			
		FA	101	2	49	26	18	22			
		FA	103	1	0	0	1	0			
		FA	103	2	44	26	15	22			
		FA	104	1	1	0	0	0			
		FA	104	2	41	25	15	20			
Spontaneous tumor pct: 22%		in ctrl. - Total		-	22	8	11	9			

Pancreas (000380):

- **insuloma (000220) + carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Pancreas	(PAN)	IN	105-105	1	3 2 0 0	0.957	0.923	0.933
Insuloma+Carcinoma	(IC)	IN	105-105	2	37 21 15 19			
Spontaneous tumor pct: 3%	in ctrl. - Total			-	3 2 0 0			

Analysis #5 (Female):

Skin (000510):

- **squamous cell carcinoma (000143) + papilloma (000300)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Skin	(SK)	IN	92-99	1	1 0 1 0	0.662	0.602	0.652
Carcinoma(squamouscell)+ Papilloma	(SCCP)	IN	92-99	2	14 8 8 5			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 1 0			

Stomach (000550) + Intestine (000220):

- **Squamous cell carcinoma (000143) + Papilloma (000300)**
- **Polyp (000320)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Stomach+Intestine	(STIN)	IN	100-100	1	0 0 1 0	0.651	0.634	0.677
Carcinoma(squamouscell)+	(SP)	IN	100-100	2	25 12 8 13			
Papilloma		FA	98	1	1 0 0 0			
		FA	98	2	29 14 13 14			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 1 0			
Stomach+Intestine(large)	(STPIN)	IN	79-91	1	1 0 0 1	0.369	0.261	0.302
Polyp	(P)	IN	79-91	2	25 15 13 11			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 1			

Liver (000280):

- **Hepatocellular Adenoma (000103) + Carcinoma (000142)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLES	EXACT PROB =P(STAT.GE.OBSERVED)	ASYMP PROB	ASYMP PROB /CONT CORR
Liver	(LIV)	IN	100-100	1	0 2 0 3	0.033	0.017	0.021
Adenoma(hepatocellular)+ Carcinoma(hepatocellular)	(HAHC)	IN	100-100	2	25 10 9 10			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 2 0 3			

Pituitary (000410):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Pituitary	(PIT)	IN	53-78	1	0 1 0 0	0.445	0.424	0.437
Adenoma+Carcinoma	(AC)	IN	53-78	2	25 10 18 17			
		IN	79-91	1	0 2 1 2			
		IN	79-91	2	26 12 12 10			
		IN	92-99	1	1 3 0 0			
		IN	92-99	2	13 5 9 5			
		IN	100-100	1	7 5 3 4			
		IN	100-100	2	18 7 6 9			
		FA	91	1	0 1 0 0			
		FA	91	2	43 20 19 18			
		FA	95	1	1 0 0 0			
		FA	95	2	33 17 18 16			
Spontaneous tumor pct: 9%	in ctrl. -	Total		-	9 12 4 6			

Thyroid (000610):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Thyroids	(THY)	IN	53-78	1	1 0 0 0	1.000	0.915	0.931
Adenoma+Carcinoma	(ADCR)	IN	53-78	2	24 11 18 17			
		IN	100-100	1	1 0 0 0			
		IN	100-100	2	24 12 9 13			
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	2 0 0 0			

Adrenal (000100):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Adrenals	(ADR)	IN	79-91	1	0 1 0 0	0.833	0.793	0.825
Adenoma+Carcinoma	(ADECAR)	IN	79-91	2	26 14 13 12			
		IN	100-100	1	1 0 0 0			
		IN	100-100	2	24 12 9 13			
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	1 1 0 0			

Parathyroids (000390):

- **Adenoma (000100) + Carcinoma (000140)**

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -------TABLES-------	EXACT PROB	ASYMP PROB	ASYMP PROB /CONT CORR =P(STAT.GE.OBSERVED)
Parathyroids	(PAR)	IN	100-100	1	2 4 0 0	0.911	0.883	0.896
Adenoma + Carcinoma	(ACAR)	IN	100-100	2	23 8 9 13			
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	2 4 0 0			