Full CAC
April 8, 1999

Attendees:

FDA: Joseph DeGeorge (HFD-024), Adele Seifried (HFD-024), Chuck Resnick (HFD-110), Glenna Fitzgerald (HFD-120), Paul Andrews (HFD-150), Dou Lucy Jean (HFD-170), Tim Robison (HFD-180), Ron Steigerwalt (HFD-510), Terry Peters (HFD-520), James Farrelly (HFD-530), Abby Jacobs (HFD-540), Andrea Weir (HFD-550), Susan Wilson (FHD-550), Baldeo Taneja (HFD-550), Sandra Cook (HFD-550), John Hyde (HFD-550), Robin Huff (HFD-570), C. Joseph Sun (HFD-570), Ken Hastings (HFD-590), Charles Anello (HFD-700), Karl Lin (HFD-715), Stan Lin (HFD-725), Joseph Contrera (HFD-901).

Merck: Bonnie Goldmann, Robert Silverman, Kamlesh Vyos, Darryl Patrick, Warren Whielods, Keith Soper, Joseph Mufetit, R.M. Perimeter, Margo Heron

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The following information reflects a brief summary of the Committee's discussion and its recommendations. Detailed study information can be found in the reviewer's background document and sponsor's background package.

NDA 21,042
Sponsor: Merck
Drug: Vioxx (refecoxib)
Indication: Anti-arthritic/analgesic

Background

Vioxx was evaluated in several genotoxicity studies [including microbial mutagenesis assay, V-79 mammalian Cell mutagenesis assay, *in vitro* and *in vivo* alkaline elution/rat hepatocyte assay, chromosomal aberrations in CHO cells, and the mouse micronucleus assay in males and females] and was considered negative by the reviewer. A subsequent evaluation by CDER's Genetic Toxicology Committee also concluded it was negative. One rat study and 2 mouse studies were conducted to address carcinogenicity. A prior ECAC concluded that although the MTD could not be definitively identified based on the data provided, the MTD was less than 10 mg/kg/day. The sponsor conducted the study using a maximum dose of 8 mg/kg, which was considered appropriate by the ECAC. The rat study was conducted using diet restriction of approximately 30%. Prior to correction for multiplicity of tests, there was a statistically significant [one-sided, age-adjusted trend test or if ≤10 tumor bearing animals a small sample, discrete, permutation test; $p < 0.05$] increase in the incidence of malignant glioma in females, pancreatic islet adenoma in males, and pancreatic acinar adenoma in

males. The incidence of malignant glioma in females was 0, 0, 4% [2/50], 0, and 6% [3/50] at 0, 0, 2, 5, and 8 mg/kg/day. The incidence of pancreatic islet adenoma was 10%[5/50], 6%[3/50], 18%[9/50], 12% [6/50] and 18% [9/50] at 0, 0, 2, 5, and 8 mg/kg/day. Pancreatic acinar adenoma was observed only in males at 8 mg/kg/day with an incidence of 4% [2/50]. After correction for multiplicity of tests, these findings were no longer statistically significant applying usual criteria. The statistics of the Sponsor were in agreement with the analyses by the FDA statistician. The analyses conducted by the FDA statistician included Peto's trend analysis [includes exact permutation trend test and continuity corrected normal test] with correction for rare vs. common tumors [e.g. significance level of 0.025 for rare tumors (rate <1%) and 0.005 for common rumors]. The sponsor did not provide historical control data from similarly diet-restricted rats to aid in the evaluation of the potential biological significance of the findings for the committee's assessment. This was considered especially important for the rare tumors.

The 2 mouse studies were initiated prior to evaluation of doses and protocol design by the ECAC. However, the selected doses, when considering both studies, covered the doses ultimately recommended by the ECAC. Based on the GI toxicity and mortality observed in the studies, the MTD was reached. There was a dose-related increase in mortality, however, it was concluded that an adequate number of animals survived in the low dose study until study termination for the study to be considered valid. In this study conducted at 5, 10, 20, and 30 mg/kg/day, there was a statistically significant increase in Harderian gland adenomas and leiomyomas in females, and lung adenocarcinomas in males. The incidence of Harderian gland adenomas in females was 4%[2/50], 8% [4/50], 4%[2/50], 10%[5/50], 2%[1/50] and 20%[10/50] at 0, 0, 5, 10, 20, and 30 mg/kg/day. The incidence of leiomyomas in females was 0, 0, 2%[1/50], 0 10%[5/50], and 2%[1/50] at 0, 0, 5, 10, 20, and 30 mg/kg/day. The incidence of lung adenocarcinomas in males was 10%[5/50], 18%[9/50], 8%[4/50], 4%[2/50], 16% [8/10] and 20%[10/50] at 0, 0, 5, 10, 20, and 30 mg/kg/day. Following correction for multiplicity of statistical tests, the increases were not statistically significant for any tumor type. The FDA statistician concurred with this conclusion. Grouping leiomyomas and leiomyosarcomas together, as is standardly done, there was a statistically significant increase in incidence at the 20-mg/kg/day dose. In the mouse study conducted at 60, 100, and 300 mg/kg/day, the mid and high dose groups were terminated early on Week 72 due to what was considered by the Sponsor as excessive mortality. The males at 60 mg/kg/day were terminated early during Week 89. The females were dosed until scheduled sacrifice during Week 104. The Sponsor indicates that there was an agreement with the Agency with respect to the premature termination. Written verification has not been provided. There was no statistically significant increase in any tumor at the 60 mg/kg/day for either males or females. The FDA statistician concurred with this conclusion.

It was noted that for both rats and mice, the increased incidences of some of these findings exceeded the available historical control ranges.

Exec CAC Discussion and Recommendations of 9/23/99:

1. There was discussion regarding the number of findings that were of low frequency showing increased incidence (e.g. malignant brain glioma in female rats and the Harderian gland adenomas and leiomyomas/leiomyosarcomas in female mice) but

generally not statistically significant after correction for multiple statistical testing. A full CAC should meet to determine the biological significance of these findings.

2. The Sponsor should provide historical control data for spontaneous background incidence of neoplasia for mice and especially for restricted feed rats. This should include data from the same testing facility over the last 5 years with individual study data as well as ranges provided.
3. It should be clarified as to the individuals involved in the agreement between the Agency and the Sponsor to prematurely terminate dose groups in the second mouse study. Written documentation should be obtained if possible.
4. It was recommended that the Genotoxicity Committee should reevaluate the genotoxicity data.

Sponsor's Presentation at the CAC

The sponsor's presentation included a review of three tumor types in mice and three in rats. The sponsor also provided new data on the background tumor rates for diet restricted rats. Their analysis for the mouse data included use of the low dose group from the high dose study. In this study the only treatment group to continue until the study termination was the low dose females.

Lung adenocarcinoma in male mice. The sponsor concluded that the findings represented a biologic variation, and were not treatment related based on:

- Incidence within historical control range and not in their view different from concurrent controls
- Incidence of adenocarcinomas at highest dose was less than concurrent control
- No increase in incidence in lung adenomas
- No evidence of an increased incidence of preneoplastic lesions

Leiomyoma/Leiomyosarcoma in female mice. The sponsor concluded that the findings represented a biologic variation, and were not treatment related based on:

- Incidence of leiomyomas at highest dose tested was less than concurrent controls and within historical control range
- Lack of dose-related increase in incidence
- No evidence of an increasing incidence of preneoplastic lesions
- No evidence of progression to malignant neoplasms

It was noted by FDA that the concurrent control findings for both the HD and LD study fell with the historical control range, but that the incidence from the mid dose group was nearly twice the historical control level. The sponsor's view that the combined incidence of leiomyomas and leiomyosarcoma was with in the historical range and thus not significant could not be evaluated as they did not report the combined incidence by study. Combining the highest incidence rates for the historical controls, the combined incidence of leiomyomas and leiomyosarcoma in the mid dose group would have just exceeded the historical control range. It was clear however, that the HD group findings were within the historical and contemporary control range.

Harderian Gland Adenomas in Female Mice. The sponsor concluded that the findings represented a biologic variation, and were not treatment related based on:
•Incidence of adenomas at highest dose tested (from the second study) was less than concurrent controls and within historical control range
•Lack of dose-related response in tumor incidence
•No evidence of an increasing incidence of preneoplastic lesions
•No progression to malignant neoplasms
•No increase in incidence in Harderian gland adenomas in male mice

FDA noted that the incidence in the mid dose group exceed all 31 control studies with the mean incidence 10-fold the average control (for the total treated groups it was more than twice the average control rate) and the low dose group exceeded the range of all but 2 historical controls. There was, however, little evidence of increased progression to malignant lesions. Total Harderian gland tumors were 2, 4, 3, 5,1,11 (for the LD study C, C, L, M, H dose groups) and 2, 4, 5 (for the HD study C, C, L dose groups).

Pancreatic Islet Adenoma in Male Rats. The sponsor concluded that the increased incidence was not treatment related based on:
•Lack of dose-related increase in incidence
•Within historical control range
•No incidence in preneoplastic lesions or malignant neoplasms

FDA noted that all treatment groups exceed the concurrent controls and all but 3 of 20 historical controls (mean of 5 in controls and 8 in treated groups per 50 animals). It was clear, however, that this was a tumor type found in all control groups and that there was a lower than expected incidence (based on historical and concurrent controls) of carcinoma. In total, there was no evidence of an increased incidence of tumors in pancreatic islet cells.

Pancreatic Acinus Adenoma in Male Rats. The sponsor concluded that this was not treatment related based on:
•Lack of dose response
•Within historical control range
•No evidence of preneoplastic lesions or malignant neoplasms

Gliomas in Female Rats. The sponsor concluded that the increased incidence was not treatment related based on:
•Lack of dose-related response in incidence
•Within historical control range
•Lack of increasing incidence with increasing systemic exposure
•No evidence of accumulation of the drug and metabolites in the brain
•No evidence of preneoplastic lesions/CNS toxicity
•Increased incidence not statistically significant. Without correction for multiplicity of testing there was high probability of a positive result
•No increase in tumor incidence in mice

It was noted that the exposure range tested would not be anticipated to provide a dose response. In response to questioning, the sponsor's statistician agreed that for rare

tumors it would not be anticipated that a dose response would be observed in a standard study design. It was noted that the incidence in the HD group exceeded all 22 historical and concurrent controls and that the low dose group exceeded all but 3 of 22 controls. A mean of 0.4 tumors per 50 animals in all 22 control groups reported with 1.7 per 50 treated animals.

The sponsor's overall conclusions were that Rofecoxib was tested up to the MTD in the rodent bioassays; the incidence of tumors observed represented biological variability; was neither a tumor initiator or promoter; there is no pharmacological basis for carcinogenic risk; and there was no stastically significant increase of any tumor type when adjusted for multiplicity in either rodent bioassay.

The FDA presentation confirmed that Rofecoxib was found by the genetox committee to be non-genotoxic under the conditions tested.

Summary of Discussion

There was discussion and some concern for immunosuppressive potential of rofecoxib. It was noted that some of the toxicology studies as well as the pharmacodynamic activity of the compound and others in this class suggested an immunosuppressive potential. It was suggested that immunosuppressive activity could have contributed to the tumor findings, although there was no consensus regarding this point. Several felt that toxicity observed in the study complicated any attribution of immunosuppression to tumor response. There was extensive discussion regarding how "rare" tumors should be evaluated and whether standard statistical approaches could be applied. It was noted that the agency has had concern for rare tumor findings for other agents, but it was noted that in those circumstances other data, such as evidence of genotoxicity, had contributed to the weight of evidence and conclusions drawn. It was agreed that if the tumors were increased as a result of rofecoxib treatment, it did not occur through a genotoxic mechanism. The committee vote and summary of comments follows:

Questions - Carcinogenicity Assessment Committee

1. Do you consider the rat carcinogenicity study to be an adequate test of the carcinogenic potential of rofecoxib? Yes – 15/15

   a. Are the doses adequate? If not, why not?

Yes 13/15 Comments:
•Mortality rates in dosed groups, especially at high-dose and GI effects and/or peritonitis.

No – 2/15 - Comments;
•High mortality especially in HD could argue that MTD was exceeded, which would reduce significance of tumor findings further.

•Exposure of dose groups was fairly close, so "dose" relationship arguments are weakened especially for rare tumors and interpretation of study results was therefore compromised.

2. Do you consider any of the tumors observed at increased incidence in rats to be of biological significance? Please provide your reasoning?

a. Malignant brain glioma in females?

Yes 3/15 - Comments:
•Although it was not statistically significant, glioma was considered rare tumor.
•It would be very unusual to observe gliomas in 2 out of 3 test groups at, or exceeding the historical rate given that it is only infrequently observed in control animals.

Maybe 4/15 – Comments:

•Possibly, because observed in 2 treated groups and a rare tumor type.
•This is an equivocal finding; appears to have an incidence greater than historical but is not excessively outside historical control range and not statistically significant.

No – 8/15 – Comments:
•Given that there was one in the spinal cord of the concurrent control, it is of questionable significance – might be equivocal.
•There was no evidence of preneoplastic; there was one found in spinal cord of concurrent control; the lack of significant drug distribution to the brain and it was only observed in females; considered together, I do not consider the finding significant.
•Given that there was no dose response incidence, even though the high-dose group was outside historical control, it may not represent a significant finding
•The finding may not be repeatable.
•At best equivocal – don't think you can conclude this is positive with such low numbers.

b. Pancreatic islet adenoma or acinar adenoma in males?

No – 15/15

3. Do you consider the mouse carcinogenicity studies to be an adequate test of the carcinogenic potential of rofecoxib?

Yes – 15/15 – Comments:
•MTD reached based on mortality

4. Should the results of both mouse studies be considered? With the lack of positive findings in the HD study, but given the mortality and premature termination of the mid and high dose animals and LD males, how do the data for the second mouse study contribute to your evaluation?

Yes – 8/15 Comments:
•The 2nd study can be used to raise confidence in the study, but should not be combined with results of the first study in analysis.
•The 2nd study causes a problem (autolysis, etc.), but does not change overall evaluation.
•The controls certainly are valid and can be used as they were continued for the full duration (females).
•Both should be considered; 2nd study reinforces the findings in 1st study and confirms MTD.
•Would use HD study controls, but I would put most emphasis on LD study for dose groups.
•Both can be considered, but only the female control and 60 mg/kg groups should be considered and used as supplementary information only. The 2nd study data should not be combined for statistical analyses.
•Labeling could include 60 mg/kg as the HD.
•The HD study provides useful information for the 60-mg/kg treatment of female mice. It supports the lack of a clear dose effect relationship for leiomyomas and Harderian gland tumors in the initial study. The HD study is of little value in aiding the interpretation of the distribution of lung carcinoma in the initial study.

No – 7/15 Comments:
•Only 1st study for males; 2nd study for females.
•Has historical control value only.
•Conclusions only based on the completed LD study.
•Only LD study is useful; 30 mg/kg is probably at least half of the MTD.

5. Do you consider any of the tumors observed at increased incidence in mice to be of biological significance? Please provide your reasoning?

a. Harderian gland adenoma in females?

No – 13/15 Comments:
•Not statistically significant, and lacking an increase in preneoplastic findings.
•Absence of a human counterpart for this organ raises question of significance for tumor findings. HD females were outside historical and concurrent controls, but the biological significance is questionable. No increase in malignant findings.

Yes – 2/15 – Comments:
•Exceeds background rate for almost all studies.

b. Uterine leiomyomas/sarcomas in females ?

No – 15/15 - **Comments:**
•Leiomyomas may be increased but this effect is not dose related.
•Highest incidence is at MD and there is no persuasive reason to negate the absence of finding at HD. Findings are near historical rate.

c. Lung adenocarcinoma in males?

No – 15/15 – **Comments:**
•Control and HD are similar. A worrisome tumor, but incidence provides no suggestion of a relationship to treatment. No increase in adenomas and no preneoplastic lesions noted. Lack of dose response and this is a relatively common tumor in mice.

6. Overall, do you conclude there is evidence of carcinogenic potential for rofecoxib? If so, on what basis?

No – 9/15 – **Comments:**
•Based on overall evaluation of the above data there is no convincing evidence.

Equivocal – 6/15 – **Comments:**
•No clear evidence of carcinogenicity, but an increased incidence of gliomas in female rats is of uncertain relationship to administration of rofecoxib.
•Some concern based on glioma and Harderian gland ademonas with concern that they exceed expected control rates.
•Overall, there are a lot of borderline findings. I would not consider this to have strong evidence. My official term would be equivocal. (Harderian and gliomas are unclear findings)

7. Are there any additional studies that should be conducted to further clarify the carcinogenic potential of rofecoxib?

No, or none listed – 12/15

Yes – 3/15 - **Comments:**
•Immunosuppression
•Testing for immunotoxicity may be appropriate.
•Re-evaluate the histology slides for the gliomas so as to subgroup them as mentioned to get a sense of true "rarity" including glioma in the control spinal cord.

/S/ 4/20/99
Joseph J. DeGeorge, Chair

Table 15 (Part I)

Selected Organs and Organ Codes for Mouse Study

9038	STOMACH PYLORUS
11044	SMALL INTESTINE DUODENUM
12000	LARGE INTESTINE
14000	LIVER
18073	PANCREAS ISLET
21000	PERITONEUM
22000	ADRENAL
22080	ADRENAL CORTEX
29000	PITUITARY
31099	THYROID PARAFOLLICULAR CELL
31413	THYROID FOLLICULAR CELL
33112	KIDNEY TUBULE
40000	OVARY
42000	UTERUS
42144	UTERUS ENDOMETRIAL STROMA
46000	VAGINA
49157	TESTIS LEYDIG CELL
49158	TESTIS RETE TESTIS
59000	SKIN
61000	MAMMARY GLAND
71000	LUNG
77000	SPLEEN
87000	SKELETAL MUSCLE
89000	BRAIN
95409	EYE HARDERIAN GLAND
98000	PRIMARY SITE UNDETERMINED

Table 15 (Part II)

Tumors and Tumor Codes for Mouse Study

60	ADENOCARCINOMA
70	ADENOMA
280	BASAL CELL TUMOR
410	CARCINOMA
780	CYSTADENOMA
1210	EPENDYMOMA
1350	FIBROSARCOMA
1570	HEMANGIOMA
1580	HEMANGIOSARCOMA
1715	HISTIOCYTIC SARCOMA
2030	LEIOMYOMA
2040	LEIOMYOSARCOMA
2050	LEUKEMIA
2095	LUTEOMA
2150	LYMPHOMA
2270	MENINGIOMA
2540	NEUROFIBROMA
2910	PAPILLOMA
3250	POLYP
3420	RHABDOMYOSARCOMA
3460	SARCOMA
3475	SCHWANNOMA
3585	SPINDLE CELL TUMOR
3610	SQUAMOUS CELL CARCINOMA
3755	THECA CELL TUMOR

Table 16 a

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend

Source: C:\VIOXX\MOUSESTUFF2\animal1.txt

Note: Dose Levels Included: CTRL LOW (0 60)
Missing value in Tumor-Caused Death is treated as tumor not causing death
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME / TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY TABLE	EXACT PROB =PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTINUITY CORR)
						1.0000	0.7117	0.7183
SMALL INTESTINE DUODENUM	(11044	IN	89-89	1	1 0			
ADENOCARCINOMA	(60)	IN	89-89	2	76 24			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0			
						1.0000	0.7117	0.7183
LARGE INTESTINE	(12000	IN	89-89	1	1 0			
LEIOMYOMA	(2030)	IN	89-89	2	76 24			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0			
						0.6686	0.4765	0.4804
LIVER	(14000	IN	89-89	1	3 1			
CARCINOMA	(410)	IN	89-89	2	74 23			
Spontaneous tumor pct: 3% in ctrl. - Total				-	3 1			
						0.7372	0.6405	0.6423
LIVER	(14000	IN	53-78	1	1 1			
ADENOMA	(70)	IN	53-78	2	6 7			
		IN	79-88	1	1 0			
		IN	79-88	2	10 3			
		IN	89-89	1	10 3			
		IN	89-89	2	67 21			
		FA	82	1	1 0			
		FA	82	2	84 27			
Spontaneous tumor pct: 13% in ctrl. - Total				-	13 4			
						1.0000	0.7117	0.7183
ADRENAL	(22000	IN	89-89	1	1 0			
SPINDLE CELL TUMOR	(3585)	IN	89-89	2	76 24			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0			
						0.5610	0.4498	0.4519
ADRENAL CORTEX	(22080	IN	89-89	1	12 4			
ADENOMA	(70)	IN	89-89	2	65 20			
Spontaneous tumor pct: 12% in ctrl. - Total				-	12 4			
						0.2376	0.0366	0.0382
THYROID PARAFOLLICULAR CE	(31099	IN	89-89	1	0 1			
ADENOMA	(70)	IN	89-89	2	77 23			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 1			
						1.0000	0.7117	0.7183
KIDNEY TUBULE	(33112	IN	89-89	1	1 0			
ADENOMA	(70)	IN	89-89	2	76 24			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0			
						0.7506	0.5799	0.5834
TESTIS LEYDIG CELL	(49157	IN	89-89	1	4 1			
ADENOMA	(70)	IN	89-89	2	73 23			
Spontaneous tumor pct: 4% in ctrl. - Total				-	4 1			
						0.4206	0.1905	0.1943
TESTIS RETE TESTIS	(49158	IN	89-89	1	1 1			
ADENOMA	(70)	IN	89-89	2	76 23			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 1			
						1.0000	0.7117	0.7183
SKIN	(59000	IN	89-89	1	1 0			
HISTIOCYTIC SARCOMA	(1715)	IN	89-89	2	76 24			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0			
						1.0000	0.7117	0.7183
SKIN	(59000	IN	89-89	1	1 0			
NEUROFIBROMA	(2540)	IN	89-89	2	76 24			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0			
						0.8296	0.7148	0.7169
LUNG	(71000	IN	53-78	1	1 1			
ADENOCARCINOMA	(60)	IN	53-78	2	6 7			
		IN	89-89	1	4 1			
		IN	89-89	2	73 23			
		FA	81	1	1 0			
		FA	81	2	87 27			
		FA	84	1	1 0			

			FA	84	2	80	27		
Spontaneous tumor pct: 7%		in ctrl. -	Total		-	7	2		
LUNG	(71000	)	IN	53-78	1	1	0	0.2001	0.1291 0.1302
ADENOMA	(70	)	IN	53-78	2	6	8		
			IN	89-89	1	7	6		
			IN	89-89	2	70	18		
			FA	37	1	1	0		
			FA	37	2	98	38		
			FA	82	1	1	0		
			FA	82	2	84	27		
Spontaneous tumor pct: 10%		in ctrl. -	Total		-	10	6		
STOMACH PYLORUS	(9038	)	IN	79-88	1	1	0	1.0000	0.6915 0.6988
ADENOMA	(70	)	IN	79-88	2	11	3		
Spontaneous tumor pct: <= 1%		in ctrl. -	Total		-	1	0		
EYE HARDERIAN GLAND	(95409	)	IN	89-89	1	12	2	0.8977	0.8141 0.8156
ADENOMA	(70	)	IN	89-89	2	65	22		
Spontaneous tumor pct: 12%		in ctrl. -	Total		-	12	2		
PRIMARY SITE UNDETERMINED	(98000	)	IN	89-89	1	1	0	0.5639	0.3552 0.3594
HISTIOCYTIC SARCOMA	(1715	)	IN	89-89	2	76	24		
			FA	81	1	1	0		
			FA	81	2	87	27		
			FA	87	1	0	1		
			FA	87	2	77	25		
Spontaneous tumor pct: 2%		in ctrl. -	Total		-	2	1		
PRIMARY SITE UNDETERMINED	(98000	)	IN	53-78	1	0	1	0.6458	0.3657 0.3705
LEUKEMIA	(2050	)	IN	53-78	2	7	7		
			FA	82	1	1	0		
			FA	82	2	84	27		
Spontaneous tumor pct: <= 1%		in ctrl. -	Total		-	1	1		
PRIMARY SITE UNDETERMINED	(98000	)	IN	89-89	1	6	0	0.9265	0.8325 0.8341
LYMPHOMA	(2150	)	IN	89-89	2	71	24		
			FA	16	1	0	1		
			FA	16	2	100	47		
			FA	78	1	1	0		
			FA	78	2	91	27		
			FA	85	1	1	0		
			FA	85	2	78	26		
Spontaneous tumor pct: 8%		in ctrl. -	Total		-	8	1		

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