NDA 21-098
Yasmin (drospirenone and ethinyl estradiol)

Pharmacology Team Leader Label Memo

Sponsor has made the requested changes in the carcinogenesis, mutagenesis, impairment of fertility and pregnancy sections that we requested. The final label is satisfactory.

Alex Jordan, PhD

NDA 21-098
HFD-580

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/s/

Alexander W. Jordan
5/14/01 02:28:07 PM
PHARMACOLOGIST

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NDA 21-098
Yasmin (drospirenone and ethinyl estradiol)

Team Leader Response to Label Comments

Re: comments by A. Jacobs.

In a memo of 2/8/01, Dr. Jacobs questioned my reason for concurring with the sponsor that the carcinogenic effects of drospirenone alone and not those of the combination of drospirenone and EE should be included in the label, specifically in reference to hepatocellular adenomas in rats. Dr. Jacobs said that they are unlikely to be due to hormonal effects. Hepatocellular tumors are a well known effect of estrogen administration to rodents. In IARC, vol 72, pg 292 there is a discussion of the effects of EE and mestranol on hepatic tumors in rats and mice. In the label for Premarin and other estrogens there is a statement that estrogens increase the frequency of carcinomas of the breast, cervix, vagina and liver in certain animal species.

Many approved estrogen/progestin oral contraceptives induce hepatic tumors in rodents (IARC vol 72). These tumors and others were omitted from the label because of the large amount of human cancer data (In the warnings section of the Yasmin and other contraceptives label, benign hepatic adenomas are listed as a possible consequence of contraceptive use). However, animal tumors that are not clearly due to estrogens or approved estrogen/progestin combinations (such as pheochromocytomas and harderian gland tumors) are included in the labeling of new progestins.

Therefore, to be consistant with labeling for other contraceptives, the data on hepatic adenomas in rats should not be included in the Yasmin label.

The comment by the exec CAC that the tumors should be included in the label specifically referred to tumors in mice and they were included (harderian gland tumors).

Alex Jordan, PhD

NDA 21-098

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/s/

Alexander W. Jordan
5/1/01 10:18:33 AM
PHARMACOLOGIST

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Comments on Yasmin (drospirenone and ethinyl estradiol) NDA 21-098

A. Jacobs 2/8/01

I have read the pharm/tox reviews and labeling comments for Yasmin and have one comment

1. It is not clear why the Pharmacology Team Leader labeling review of 5/30/00 concurs with the sponsor that the carcinogenicity effects of drospirenone alone and not those of the combination of drospirenone and ethinyl estradiol would be included in the labeling. In particular hepatocellular adenomas in rats were seen with the combination product as well as with ethinyl estradiol alone and are unlikely to be due to hormonal effects. Furthermore, the exec-CAC of 1/14/00 recommended that "the tumors observed should be reported." It seems appropriate that the hepatocellular adenomas seen in rats be described in the labeling.

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/s/

Jeanine Best
4/18/01 01:35:45 PM
CSO
Memo sent via e-mail from A. Jacobs, Pharmacology/Toxicology ODE III [
Office Level Sign-off]

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JUN 07

NDA 21-098 6/7/00

Pharmacology Team Leader Memo

Drug: Yasmin (drospirenone + ethinyl estradiol)

Apparently, the Sponsor (Berlex) never received the minutes from the January 4, 2000 executive CAC meeting. Those minutes stated that the rat carcinogenicity study was considered acceptable if the AUC data are valid. It went on to say that the sponsor should provide evidence that the extrapolation from $AUC_{0\text{-}4h}$ to $AUC_{0\text{-}24h}$ is valid.

Although I accepted the carcinogenicity study without a response, the sponsor stated that the extrapolation information was submitted in the original NDA. I have appended the data to get it into the record. The data provide satisfactory evidence that the $AUC_{0\text{-}4h}$ to $AUC_{0\text{-}24h}$ extrapolation is valid.

/S/

Alex Jordan, PhD

Orig NDA 21-098
HFD-580
Jbest/AJordan

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Fly Sheet 2: Synopsis

1. Introduction

During the past decade a number of repeated dose toxicity studies have been conducted with drospirenone (DRSP) in mice, rats and monkeys which all included a more or less extensive concomitant drug plasma level monitoring and an estimation of relative exposure versus human exposure levels (according to the respective state of knowledge) was generally attempted if possible. However, in the mean-time new knowledge concerning animal and human exposure levels of drospirenone has been gained which requires an overall reevaluation of the available toxicokinetic data base.

For example, further human pharmacokinetic data have become available (reports A470 and AI98) which are considered to reflect more accurately the human steady-state exposure after repeated daily intake of 3 mg drospirenone in combination with 30 µg ethinylestradiol (EE_2) than earlier data (e.g. report 8235) which were obtained after single administration of 2 mg DRSP and which were considered for the choice of dose levels for the first repeated dose toxicity studies in rats (report 8716) and monkeys (report 8717).

Due to this history of preclinical drospirenone development, a critical appraisal and reevaluation of the overall toxicokinetic data base has become necessary.

The situation is further complicated by the fact that the metabolic degradation of drospirenone in the plasma of rats and mice after sample collection has been discovered rather late during drug development. This in vitro instability, however, became known prior to the start of the 3-month toxicity study in mice (report AG46) and thus could be prevented by the addition of an inhibitor to the blood samples. Inhibition of the in vitro degradation in rat samples was also performed at terminal sacrifice in the rat carcinogenicity study (report AG75). Only these rat data are, therefore, considered adequate for estimation of relative exposure in the rat compared to human steady-state exposure.

In the following, a reevaluation of animal relative exposure data according to the present state of knowledge will be given which is based on a single human "reference exposure".

2. DRSP exposure estimations in toxicological studies

According to a current publication [1] describing FDA requirements for nonclinical testing of contraceptive steroids, pharmacokinetic parameters should be determined under steady-state conditions in rats, monkeys and humans in order to be able to compare exposures rather than doses for interspecies comparisons. Pharmacokinetics should include (among other parameters) the determination of the area under the drug concentration versus time curve without further specification whether this should be the total area from dosing time extrapolated to infinity (AUC) or the area within a dosage interval (AUC(0-τ)).

In general, the AUC determined after single administration is proportional to the dose and is used as a measure for the systemic drug exposure under these conditions. Under the conditions of linear pharmacokinetics, the AUC(0-τ) determined at steady state after chronic administration is identical to the AUC determined after single administration and thus the AUC(0-τ) should be used as a measure of systemic exposure under steady state conditions.

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Fly Sheet 2: Synopsis (cont'd)

which also complies with common practice.

With regard to the experimental data available for the estimation of the systemic exposure to DRSP achieved in mice and rats, a direct comparison of animal and human data is not feasible as they are different with respect to the quality of the database used for AUC assessment. While the animal data were obtained during toxicological studies and represented therefore a compromise between an optimized blood sampling schedule as would be applied for a pure pharmacokinetic study and a limited blood sampling schedule as would be preferred in toxicological studies, the human data were obtained with an optimized blood sampling scheme.

For an appropriate comparison, the AUC data determined in the toxicological studies, which are mostly partial areas representing only a certain fraction of the AUC within a dosage interval (i.e. of the AUC(0-24h)), were multiplied by a correction factor in order to estimate the AUC(0-24h) which would have been obtained if the blood sampling scheme had been optimized. This correction factor was calculated as fraction (area percentage) of the AUC(0-24h) for the respective dose level taking additional data from separate pharmacokinetic studies into consideration which were based on an adequate number of sampling points. Based on these fractions and the partial areas AUC(0-t) which were actually determined in the toxicological studies, the theoretical AUC(0-24h) was extrapolated for each dose level. In order to put these exposure data in animals into perspective with the exposure to the drug in humans, the extrapolated AUC(0-24h) was divided by the respective mean AUC(0-24h) value determined under steady-state conditions in humans. The human reference AUC(0-24h) data were obtained by considering all available pharmacokinetic data obtained after repeated daily administration of the anticipated oral contraceptive dose (3 mg DRSP + 0.03 mg EE_2) over at least 3 treatment cycles. Based on the data summarized in reports A470 and AI98, an overall mean DRSP AUC(0-24h) of 917 ng·h/ml was calculated (Table 1).

Table 1: Mean (± standard deviation) DRSP AUC(0-24h) values obtained after repeated daily administration of 3 mg DRSP + 30 µg EE_2 to healthy young women.

Reference	DRSP AUC(0-24h) [ng·h/ml]	No. of subjects	Duration of treatment [cycles]
A470	814 ± 268	34	3
AI98	930 ± 175	12	6
AI98	957 ± 216	12	9
AI98	968 ± 230	12	13
Overall mean	917	–	–

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Fly Sheet 2: Synopsis (cont'd)

Studies in rats

Exposure data of DRSP in rats were obtained in 3 toxicological studies and the respective AUC(0-4h) values of DRSP determined in these studies were summarized in reports 9374, A467 and AG75. In two of these studies (reports 9374 and A467), DRSP was not stabilized in blood samples which led to an underestimation of the true exposure relative to the values obtained in the third study (report AG75). However, these data were included in the present reevaluation, as they give an estimate of the drug exposures which have at least been achieved.

According to the data obtained in a pharmacokinetic study with DRSP in female rats (report AF68), the AUC(0-4h) recalculated with those time points used in the toxicological studies represented 60 % and 38 % of the AUC(0-24h) after administration of 1 mg and 10 mg DRSP/kg, respectively (Table 2). Using these area percentages and the measured AUC(0-4h) values reported in reports 9374 and A467, the corresponding AUC(0-24h) values were calculated which theoretically should have been achieved with a more appropriate sampling schedule (Tables 3 and 4). For calculation of the respective value after administration of 3 mg/kg, the area percent value determined after administration of the 1 mg/kg dose (60 %) was used.

In the third study (report AG75), the AUC(0-24h) could be established at the end of the 2 years treatment period using a sampling schedule with 6 time points. Under these conditions, the AUC(0-24h) values measured represented about 98 % and 91 % of the AUC(0-24h) determined in report AF68 after administration of 1 and 10 mg/kg, respectively. Based on these data, the values shown in Table 4 were calculated. The relative systemic exposures (multiples of human exposure) are summarized in Table 5.

Table 2: AUC values [ng·h/ml] of DRSP in female rats (recon AF68)

Parameter	Dose 1.0 mg/kg/d		Dose 10 mg/kg/d	
	Measured value	Fraction of AUC(0-24h)	Measured value	Fraction of AUC(0-24h)
AUC(0-24h)	510	100%	8641	100%
AUC(0-4h)*	304	60%	3276	38%
AUC(0-24h)*	500	98%	7830	91%

*: Data from AF68 recalculated with timepoints 0, 1, 2, 4, 8, 12, 24h as used in rat tox. studies with DRSP/EE2

Fly Sheet 2: Synopsis (cont'd)

Table 3: Evaluation of the systemic DRSP exposure in female rats in a 3 months tolerance study (report 9374). AUC-values are given in ng·h/ml

Treatment period	Drug administered	Dose 1.0 mg/kg/d		Dose 3.0 mg/kg/d		Dose 10.0 mg/kg/d	
		Measured AUC(0-4h)	Extrapolated AUC(0-24h)	Measured AUC(0-4h)	Extrapolated AUC(0-24h)	Measured AUC(0-4h)	Extrapolated AUC(0-24h)
2 weeks	DRSP	203	341	707	1186	2030	5354
13 weeks	DRSP	256	429	917	1538	2770	7306
2 weeks	DRSP + EE2	233	391	629	1055	1580	4168
13 weeks	DRSP + EE2	208	349	684	1148	2250	5935

Table 4: Evaluation of the systemic DRSP exposure in female rats in a one year tolerance study (report A467) and a two year tumorigenicity study (report AG75). AUC-values are given in ng·h/ml

Treatment period [Report No.]	Drug administered	Dose 0.3 mg/kg/d		Dose 3.0 mg/kg/d		Dose 10.0 mg/kg/d	
		Measured AUC data	Extrapolated AUC(0-24h)	Measured AUC data	Extrapolated AUC(0-24h)	Measured AUC data	Extrapolated AUC(0-24h)
[A467]		AUC(0-4h)		AUC(0-4h)		AUC(0-4h)	
27 weeks	DRSP + EE2	95	159	677	1136	2067	5452
1 year	DRSP + EE2	93	156	594	997	1947	5136
[AG75]		AUC(0-24h)		AUC(0-24h)		AUC(0-24h)	
2 years	DRSP	472	481	3154	3217	9644	10643
2 years	DRSP + EE2	760	775	2983	3043	7962	8787

Fly Sheet 2: Synopsis (cont'd)

Table 5: Evaluation of the relative systemic DRSP exposure (AUC(0-24h) ratio)

Treatment period [Report No.]	Drug administered	AUC(0-24h) ratio Rat/Human at DRSP doses of 0.3 mg/kg/d	1.0 mg/kg/d	3.0 mg/kg/d	10.0 mg/kg/d
[9374]					
2 weeks	DRSP	n.d.	0.4	1.3	5.8
13 weeks	DRSP	n.d.	0.5	1.7	8.0
2 weeks	DRSP + EE2	n.d.	0.4	1.2	4.5
13 weeks	DRSP + EE2	n.d.	0.4	1.3	6.5
[A467]					
27 weeks	DRSP + EE2	0.2	n.d.	1.2	5.9
1 year	DRSP + EE2	0.2	n.d.	1.1	5.6
[AG75]					
2 years	DRSP	0.5	n.d.	3.5	11.6
2 years	DRSP + EE2	0.8	n.d.	3.3	9.6

n.d.: no data available

Studies in monkeys

Monkey exposure data were obtained at the end of a one year tolerance study (report A456). In this case, AUC(0-24h) values were directly determined with an appropriate sampling schedule, since recalculation of single dose data from a pharmacokinetic study with those time points reported in report A456 revealed that the AUC(0-24h) values determined after administration of 1 and 10 mg DRSP/kg differed by 2 and 1 %, respectively, as compared to the data obtained with an optimized sampling schedule. Therefore, no corrections were made for the comparison of monkey and human AUC(0-24h) values. The results shown in report A456 and the calculated multiples of human exposure are shown in Table 6.

Fly Sheet 2: Synopsis (cont'd)

Table 6: Evaluation of the relative systemic DRSP exposure in female monkeys (report A456). AUC-values are given in ng·h/ml

Treatment period	Drug administered	Measured AUC(0-24h) at DRSP doses of [mg/kg/d]			AUC(0-24h) ratio Monkey/Human at DRSP doses of [mg/kg/d]		
		0.3	3.0	10	0.3	3.0	10
1 year	DRSP	n.d.	8239	20675	n.d.	9.0	22.5
1 year	DRSP + EE2	1030	7606	28517	1.1	8.3	31.1

n.d.: no data available

Studies in mice

Exposure data of DRSP in mice were obtained from two toxicological studies (reports AG46 and AW44) and one pharmacokinetic study (report A705).

Similar to the calculations performed with rat data as described above, the AUC(0-4h) data obtained for DRSP in mice in one toxicological study (report AG46) were transformed to the respective AUC(0-24h) data. The area percentages used for that purpose are summarized in Table 7.

In the case of the tumorigenicity study (report AW44), the AUC(0-4h) was determined after one and two years of treatment. In addition, the AUC(0-24h) was determined using an appropriate sampling schedule after two years of treatment. Since a different mouse strain was used in this study as compared to the pharmacokinetic study, the AUC(0-4h) values determined after one year of treatment were extrapolated to AUC(0-24h) values based on the area percentages determined at the end of the study. The respective data are shown in Table 9.

Finally, the measured or extrapolated AUC(0-24h) values were compared to the mean human AUC(0-24h) value, the result of which is summarized in Table 10.

Table 7: AUC values [ng·h/ml] of DRSP in female mice (report A705)

Parameter	Dose 3.0 mg/kg/d		Dose 10.0 mg/kg/d		Dose 30.0 mg/kg/d	
	Measured value	Fraction of AUC(0-24h)	Measured value	Fraction of AUC(0-24h)	Measured value	Fraction of AUC(0-24h)
AUC(0-24h)	85	100%	893	100%	8401	100%
AUC(0-4h)	67	79%	757	85%	6039	72%
AUC(0-4h)*	84	99%	817	91%	6802	81%

*: Data from report A705 recalculated with time points 0, 0.5, 1, 4h as used in one mouse study (report AG46) after DRSP administration. Following administration of DRSP + EE_2, AUC(0-4h) values were calculated as in report A705 with time points 0, 0.5, 1, 2, 4 h

Fly Sheet 2: Synopsis (cont'd)

Table 8: Evaluation of the systemic DRSP exposure in female mice in a 3 months tolerance study (report AG46). AUC-values are given in ng·h/ml

Treatment period	Drug administered	Dose 3.0 mg/kg/d		Dose 10.0 mg/kg/d		Dose 30.0 mg/kg/d	
		Measured AUC(0-4h)	Extrapol. AUC(0-24h)	Measured AUC(0-4h)	Extrapol. AUC(0-24h)	Measured AUC(0-4h)	Extrapol. AUC(0-24h)
14 weeks	DRSP	116	117	1204	1316	7862	9710
14 weeks	DRSP + EE2	66	84	435	513	2684	3734

Table 9: Evaluation of the systemic DRSP exposure in mice in a 2 years tumorigenicity study (report AW44). AUC-values are given in ng·h/ml

Treatment period	Drug administered	Dose 1.0 mg/kg/d		Dose 3.0 mg/kg/d		Dose 10.0 mg/kg/d	
		AUC(0-4h)	AUC(0-24h)	AUC(0-4h)	AUC(0-24h)	AUC(0-4h)	AUC(0-24h)
1 year	DRSP	79.5	105*	351	413*	1733	2241*
1 year	DRSP + EE2	49.9	63.6*	331	390*	1714	2216*
2 years	DRSP	53.7	70.7	285	336	2050	2650
2 years	DRSP + EE_2	39.4	50.2	n.d.	n.d.	1653	2147*

*: extrapolated values n.d.: no data available

Table 10: Evaluation of the relative systemic exposure (AUC(0-24h) ratio mouse/human).

Treatment period [Report No.]	Drug administered	AUC(0-24h) ratio Mouse/Human at dose levels of			
		1.0 mg/kg/d	3.0 mg/kg/d	10 mg/kg/d	30 mg/kg/d
[AG46]					
14 weeks	DRSP	n.d.	0.1	1.4	10.6
14 weeks	DRSP + EE2	n.d.	0.1	0.6	4.1
[AW44]					
1 year	DRSP	0.1	0.5	2.4	n.d.
1 year	DRSP + EE2	0.1	0.4	2.4	n.d.
2 years	DRSP	0.1	0.4	2.9	n.d.
2 years	DRSP + EE2	0.1	n.d.	2.3	n.d.

n.d.: no data available

JUN 06

NDA 21-098 5/30/00

Pharmacology Team Leader Label Review

Drug: Yasmin (drospirenone)

The Sponsor submitted a response to our labeling comments in a 5/9/00 Amendment. This review addresses their response as well as including statements about the label in general.

The comparison between the exposures in animals and humans are based on AUC's of drospirenone and are accurate based on the submission of 2/15/00.

I agree with the Sponsor that since the pituitary adenomas in mice and hepatocellular adenomas in rats occurred with essentially equal incidence in the drospirenone plus ethinyl estradiol groups and the ethinyl estradiol alone groups and not in the drospirenone alone groups, these tumors are due to the effect of estrogen only and need not be included in the label.

Sponsor submitted historical control data on the incidence of visceral anomalies and dilated renal pelves in Han:Wistar rats in a 5/24/00 fax. There is a wide range with several studies having incidences in the control rats greater that the 6% incidence in rats given drospirenone in this study. Therefore I agree that this result should be removed from the label.

The Sponsor claims that the effects seen in the rat and rabbit teratology studies occurred in the presence of maternal toxicity. This was based on dubious interpretation of the body weight gain data. There was a significant decrease from controls in BW gain in rats between days 6-15 but not at other time points and final body weight gains and body weights were the same between treated and controls. In rabbits the only significant difference between treated and controls was a decrease in maternal carcass weight (body weight minus weight of uterus and contents) in the mid-dose, but not high-dose group). I feel that the claim of maternal toxicity should be removed.

The Sponsor had the harderian gland tumor data re-evaluated at [redacted] he [redacted] The quality control signed GLP study found two fewer harderian gland carcinomas (1 instead of 3 in the HD group) which made the tumors nonsignificant. I have no way of knowing if the reread is more accurate that the original. However, I recommend retaining the results in the label for the following reasons. First, it is not clear why the slides were re-examined and whether the second read is more accurate than the first. Second, the sponsor asked that the trend test not be used by [redacted] a protocol violation. The time-to-tumor analysis (pg 0080), of benign and malignant adenocarcinomas (harderian glands) had a p value of 0.062 using a one-sided pairwise comparison with the control. A trend test may have been statistically significant even after the reevaluation of the slides. Third, only the slides with positive results were reread. This is extremely biased since the most likely outcome is a decrease in the number of tumors. Forth, the carcinogenicity study used very low doses so no possible tumorigenicity effect should be overlooked.

Recommendation: The histopathology from the mouse carcinogenicity study (Report AZ86) and the re-examination (submission of 5/4/00, safety update) that was performed b[redacted], be audited.

/S/

Alex Jordan, PhD

6/6

NDA 21-098
HFD-580
HFD-345
AJordan

APPEARS THIS WAY
ON ORIGINAL

Memorandum

Date: 16 March 2000

From: David E. Morse, Ph.D. /S/
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D., Director, Office of Drug Evaluation III
Victor Raczkowski, M.D., Deputy Director, Office of Drug Evaluation III

Cc: Marianne Mann, M.D., Dep. Dir., HFD-580
Alex Jordan, Ph.D., TL Pharm./Tox., HFD-580

Subject: NDA 21-098
YASMIN® Contraceptive Tablets
Ethinyl estradiol (30 μg) and Drospirenone (3 mg) oral tablet
Review of Pharm./Tox. Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-098, 11 Feb. 2000, written by Krishan L. Raheja, DVM, Ph.D.
2. Pharm./Tox. TL Memoranda for NDA 21-098, written by Alex Jordan, Ph.D (28 Feb. 2000) and Karen Davis-Bruno, Ph.D. (14 Feb. 2000).
3. NDA 21-098 Approval Package, with Draft Product Labeling (dated 29 Feb. 2000).

II. Comments and Conclusions

1. A review of the action package for NDA 21-098, YASMIN® Tablets, suggests that the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies including 2-year carcinogenicity studies, for approval of the requested indication (prevention of pregnancy in women who elect to use an oral contraceptive).

2. In accordance with current labeling practice for hormonal contraceptive agents, in the Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy sections of the proposed (draft) product label, reference should be made to the relevant sub-sections of Warnings and Contraindications which contain summary risk evaluations of carcinogenic and reproductive effects evaluated in epidemiology studies of hormonal contraception.

   In accordance with current labeling practice for all hormonal contraceptive agents, YASMIN® Contraceptive Tablets has been designated Pregnancy Category "X".

3. Consideration should be given to the inclusion of information on breast milk drug concentration and neo-natal drug exposure in woman taking hormonal contraceptives during lactation.

4. Specific comments related to the product label follow:
   - Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:

- the genotoxicity studies conducted with drospirenone be identified and described as having been conducted "in vitro" or "in vivo" as is appropriate for each study methodology,
- the basis for the interspecies dose comparisons presented in the Carcinogenesis section of the product label should be provided (i.e., AUC, body-surface area, etc.)
- the description of drug doses in the mouse and rat carcinogenicity studies should be revised to clarify that drospirenone and ethinyl estradiol were studied individually and in combination (further, it is recommended that the description of combination drug treatment regimens be presented in a similar manner in both the Carcinogenesis and Pregnancy sections of the product label [i.e., specify doses or 100:1 ratio]), and
- reference to the "retro-orbital gland not [being] present in humans" be deleted from the product label.

- Under the heading of "Pregnancy Category" it is recommended that:
  - the basis for the interspecies dose comparisons presented in this section of the product label should be provided (i.e., AUC, body-surface area, etc.), and
  - reference to "delayed ossification of feet bones" be reworded as "bones of the feet" or revised to specify the affected bones.

III. Summary

Review of the action package for NDA 21-098, YASMIN®, suggests that the product has been adequately evaluated in multiple non-clinical safety studies (including carcinogenicity studies with the combination product) for approval of the requested indication (use as an oral contraceptive agent).

The proposed product label, with possible revision as suggested in the preceding section of this memorandum, adequately reflects the safety data for this product.

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FEB 28 2000

Pharmacology Review of Package Insert

This review supercedes my previous labeling memo. It incorporates information submitted by the sponsor in response to my questions.
The label should be revised to read as follows:

9. CARCINOGENESIS
See WARNINGS Section
In a 24 month oral carcinogenicity study in mice dosed with 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.1 to 2 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was a significant dose related increase in pituitary adenomas in mice receiving the combination and a dose related increase in carcinomas of the harderian gland in the group that received drospirenone alone. In a similar study in rats given 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 0.4 to 10 times the exposure of women taking a contraceptive dose, there was a significant positive dose response in hepatocellular adenomas of the liver and an increased incidence of benign and benign and malignant adrenal gland pheochromocytomas in the group receiving the high dose drospirenone alone. Drospirenone was not mutagenic in a number of in vitro and in vivo bacterial and mammalian genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA.

10. PREGNANCY
Pregnancy category X. See CONTRAINDICATIONS and WARNINGS Sections.
A teratology study in pregnant rats given drospirenone orally at doses of 5, 15 and 45 mg/kg/day, 6 to 50 times the human exposure, resulted in an increase in the number of fetuses with delayed ossification of feet bones in the two higher doses and a slight increase in the number of fetuses with visceral anomalies, primarily severely dilated renal pelves, at the high dose only. A similar study in rabbits dosed orally with 1, 30 and 100 mg/kg/day drospirenone, 2 to 27 times the human exposure, resulted in an increase in fetal loss and retardation of fetal development (delayed ossification of small bones, multiple fusions of ribs) at the high dose only. When drospirenone was administered with ethinyl estradiol (100:1) during the period of genital development at doses of 5, 15 and 45 mg/kg, there was a dose dependent increase in feminization of male rat fetuses. In a study with a small number of cynomolgous monkeys, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinyl estradiol (100:1) at doses up to 10 mg/kg/day drospirenone, 30 times the human exposure.

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I used the sponsors AUC data from the rat and mouse carcinogenicity studies. For the reproductive studies, I used the PK information recently submitted in response to my questions.

/S/ 2/28

Alex Jordan, PhD

NDA 21-098
HFD-580
AJordan/JBest

APPEARS THIS WAY
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TABLE 3: Comparison of Pharmacokinetic Parameters in Mice, Rats and Humans (Cont'd)

Species:	Rat						Human			
Report Number	9374 [P4] (Week 2)						A470 (N=34) 3 cycles	AI98 (N=12) 6 cycles	AI98 (N=12) 9 cycles	AI98 (N=12) 13 cycles
Dose (mg/kg/day)	1.0 DRSP	3.0 DRSP	10.0 DRSP	1.0 DRSP + 0.01 EE_2	3.0 DRSP + 0.03 EE_2	10.0 DRSP + 0.1 EE_2	(3.0 mg DRSP + 30 µg EE_2/day) AUC (0-24) [ng•h/mL]$_{measured}$ Overall mean = 917 ng•h/mL			
AUC (0-4) [ng•h/mL]	203	707	2030	233	629	1580				
AUC (0-24)$_{extrapolated}$ *	341	1186	5354	391	1055	4168	814 (268)	930 (175)	957 (216)	918 (230)
C_{max} (ng/mL)	77	236.4	686.8	76.8	207.6	644.4	60.4 (20.09)	84.2 (16.2)	81.3 (15.5)	78.7 (14.4)
T_{max} (hours)	1.0	2.0	1.0	2.0	1.0	1.0	2.7 (1.4)	1.8 (0.3)	1.6 (0.6)	1.6 (0.4)
Multiple of Human Exposure	0.4	1.3	5.8	0.4	1.2	4.5				
Report Number	9374 [P5] (Week 13)									
Dose (mg/kg/day)	1.0 DRSP	3.0 DRSP	10.0 DRSP	1.0 DRSP + 0.01 EE_2	3.0 DRSP + 0.03 EE_2	10.0 DRSP + 0.1 EE_2				
AUC (0-4) [ng•h/mL]	256	917	2770	208	684	2250				
AUC (0-24)$_{extrapolated}$ *	429	1538	7306	349	1148	5935				
C_{max} (ng/mL)	98.5	304.8	866.4	86.4	268.8	858				
T_{max} (hours)	2.0	2.0	2.0	2.0	2.0	2.0				
Multiple of Human Exposure	0.5	1.7	8.0	0.4	1.3	6.5				
Report Number	AG75 [P4] (Weeks 105 to 107)									
Dose (mg/kg/day)	0.3 DRSP	3.0 DRSP	10.0 DRSP	0.3 DRSP+ 0.003 EE_2	3.0 DRSP + 0.03 EE_2	10.0 DRSP + 0.1 EE_2				
AUC (0-4) [ng•h/mL]	234	1111	3090	445	1143	2680				
AUC (0-24)$_{extrapolated}$ *	481	3217	10643	775	3043	8787				
C_{max} (ng/mL)	122	482	1203	228	370	850				
T_{max} (hours)	2	1	1	2	1	4				
Multiple of Human Exposure	0.5	3.5	11.6	0.8	3.3	9.6				

AUC(0-24) = area under the plasma concentration-time curve from 0 to 24 hours
AUC (0-∞ [ng•h/mL] = area under the plasma concentration-time curve from 0 to infinity
C_{max} (ng/mL) = maximum concentration of drug in serum after drug administration
T_{max} (hours) = time to reach maximum serum concentration of drug following drug administration
Multiple of Human Exposure = Ratio of AUC (0-24)$_{extrapolated}$ rodent / [917 ng•h/mL] (Mean AUC(0-24)$_{human}$)

N.D. = Value not determined
[P5] = Pooled plasma from 5 animals, [P4] = Pooled plasma from 4 animals, [P2,3] = Pooled plasma from 2 or 3 animals; individual animal values are not determined the mouse or rat studies with toxicokinetics
* = AUC (0-24)$_{extrapolated}$ values (Summarized in Report AW45) are considered equal to AUC (0-∞) because DRSP plasma levels fell below the level of detection prior to 24 hours after dosing

030

TABLE 3: Comparison of Pharmacokinetic Parameters in Mice, Rats and Humans

Species:	Mouse						Human			
Report Number	AG46 [P4] (Week 14)						A470 (N=34) 3 cycles	AI98 (N=12) 6 cycles	AI98 (N=12) 9 cycles	AI98 (N=12) 13 cycles
Dose (mg/kg/day)	3.0 DRSP	10.0 DRSP	30.0 DRSP	3.0 DRSP + 0.03 EE,	10.0 DRSP +0.1 EE,	30.0 DRSP +0.3 EE,	(3.0 mg DRSP + 30 µg EE/day)			
AUC (0-4) [ng•h/mL]	116	1204	7862	66	435	2684				
AUC (0-24)$_{\text{extrapolated}}$ *	117	1316	9710	84	513	3734	814 (268)	930 (175)	957 (216)	968 (230)
C_{max} (ng/mL)	108	718	4110	52.8	501	2460	60.4 (20.09)	84.2 (16.2)	81.3 (15.5)	78.7 (14.4)
T_{max} (hours)	0.5	0.5	0.5	0.5	0.5	0.5	2.7 (1.4)	1.8 (0.3)	1.6 (0.6)	1.6 (0.4)
Multiple of Human Exposure	0.1	1.4	10.6	0.1	0.6	4.1				
Report Number	AW44 [P4] (Week 53)									
Dose (mg/kg/day)	1.0 DRSP	3.0 DRSP	10.0 DRSP	1.0 DRSP + 0.01 EE,	3.0 DRSP + 0.03 EE,	10.0 DRSP + 0.1 EE,				
AUC (0-4) [ng•h/mL]	79.5	351	1733	49.9	331	1714				
AUC (0-24)$_{\text{extrapolated}}$ *	105	413	2241	63.6	390	2216				
C_{max} (ng/mL)	44	207	666	36.6	313	970				
T_{max} (hours)	1.0	0.5	0.5	0.5	0.5	0.5				
Multiple of Human Exposure	0.1	0.5	2.4	0.1	0.4	2.4				
Report Number	AW44 [P2,3] (Weeks 106 to 107)									
Dose (mg/kg/day)	1.0 DRSP	3.0 DRSP	10.0 DRSP	1.0 DRSP + 0.01 EE,	3.0 DRSP + 0.03 EE,	10.0 DRSP + 0.1 EE,				
AUC (0-4) [ng•h/mL]	53.7	285	2050	39.4	N.D.	1653				
AUC (0-24)$_{\text{extrapolated}}$ *	70.7	336	2650	50.2	N.D.	2147				
C_{max} (ng/mL)	41.1	245	1069	42.6	196	1178				
T_{max} (hours)	0.5	0.5	0.5	0.5	0.5	0.5				
Multiple of Human Exposure	0.1	0.4	2.9	0.1	N.D.	2.3				

AUC(0-24) = area under the plasma concentration-time curve from 0 to 24 hours
AUC (0-∞) [ng•h/mL] = area under the plasma concentration-time curve from 0 to infinity
C_{max} (ng/mL) = maximum concentration of drug in serum after drug administration
T_{max} (hours) = time to reach maximum serum concentration of drug following drug administration
Multiple of Human Exposure = Ratio of AUC (0-24)$_{\text{extrapolated}}$ rodent / [917 ng•h/mL] (Mean AUC(0-24)$_{\text{human}}$)

N.D. = Value not determined
[P5] = Pooled plasma from 5 animals, [P4] = Pooled plasma from 4 animals, [P2,3] = Pooled plasma from 2 or 3 animals; individual animal values are not determined the mouse or rat studies with toxicokinetics
* = AUC (0-24)$_{\text{extrapolated}}$ values (Summarized in Report AW45) are considered equal to AUC (0-∞) because DRSP plasma levels fell below the level of detection prior to 24 hours after dosing

FEB 14 2000

NDA 21-098
Yasmin (drospirenone)

Karen Davis-Bruno PhD.
2/14/00

Acting Pharmacology Team Leader Review of Package Insert NDA 21-098

Animal Pharmacology and/or Toxicology section should be revised as follows:

Paragraph 2: Drospirenone was not a gene mutagen in a standard battery of bacterial and mammalian cell mutagenicity assays conducted in the presence and absence of metabolic activation. [Reports 8467, 8494, 9211, 9313, 8495, 8724]. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA.

Paragraph 3: In a 24 month oral carcinogenicity study in mice dosed with 1+0.01, 3 + 0.03 and 10+ 0.1 mg/kg/day of drospirenone and ethinyl estradiol, which is 0.01 to 0.4 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, a significant dose related increase in pituitary adenomas occurred in mice receiving the combination and a dose related increase in carcinomas of the harderian gland occurred in the group receiving drospirenone alone.

A similar study in rats given 0.3+0.003, 3+ 0.03 and 10+ 0.1 mg/kg/day drospirenone and ethinyl estradiol, which is 0.07 to 4 times the exposure of women taking a contraceptive dose, resulted in a significant, positive dose response in hepatocellular adenomas of the liver and increased incidence of benign and malignant adrenal gland pheochromocytomas in the high dose group receiving drospirenone alone.

Paragraph 4: Estrogens and progestins should not be used during pregnancy. Oral administration of drospirenone to pregnant rats or rabbits during organogenesis at doses up to 45 mg/kg/day in rat or 100 mg/kg/day in rabbits (17 and 8 times, respectively, the exposure of women taking a contraceptive dose), resulted in an increase in fetal loss and retardation of fetal development in rabbits and slight retardation of development (delayed ossification of footbones) and slight increase in fetuses with visceral anomalies in rats. A dose dependent increase in feminization of male rat fetuses was observed. In a cynomolgus monkey study with a small number of animals, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinyl estradiol (100:1) at doses up to 10 mg/kg/day which is 11 times the exposure of women taking a contraceptive dose.

Best

FEB 11 2000

NDA 21-098
Yasmin (drospirenone)

Pharmacology Team Leader Review of NDA 21-098

Dr. Raheja's review is complete and I agree with the conclusions. The data on pharmacokinetics are somewhat confusing and the multiples of the human dose could be quite different depending on which data are chosen but the overall conclusion on drug safety is reasonable. The one issue that has not been addressed is the request from the executive CAC to provide evidence that the extrapolation of drug blood levels in rats is valid. From the ADME summary and the human blood drug levels from the label, it seems clear that the extrapolation is not valid and the multiples of the human exposure are incorrect in any case. The rat carcinogenicity study almost certainly does not meet the criteria for acceptability according to the ICH document on carcinogenicity testing. Because of what is known about contraceptive steroids from prior human experience and previous animal tests and the submitted data from the rat and mouse studies which do not raise any extraordinary concerns, I feel that Yasmin should be approved without any additional information from the Sponsor. It should be noted that most of the previous contraceptive steroids were tested in rodents at exposure below the exposure of women taking a contraceptive dose.

The label should be revised to read as follows:

9. CARCINOGENESIS
See WARNINGS Section
In a 24 month oral carcinogenicity study in mice dosed with 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.01 to 0.4 times the exposure (AUC of drospirenone) of women taking a contraceptive dose, there was a significant dose related increase in pituitary adenomas in mice receiving the combination and a dose related increase in carcinomas of the harderian gland in the group that received drospirenone alone. In a similar study in rats given 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 0.07 to 4 times the exposure of women taking a contraceptive dose, there was a significant positive dose response in hepatocellular adenomas of the liver and an increased incidence of benign and benign and malignant adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone alone. Drospirenone was not mutagenic in a standard battery of genotoxicity tests with and without metabolic activation. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA.

10. PREGNANCY
Pregnancy category X. See CONTRAINDICATIONS and WARNINGS Sections.
Oral administration of drospirenone to pregnant rats or rabbits during the period of organogenesis at doses up to 45 (rats) or 100 mg/kg/day (rabbits), 17 and 8 times, respectively, the exposure of women taking a contraceptive dose, resulted in an increase in fetal loss and retardation of fetal development in rabbits and slight retardation of development (delayed ossification of feetbones) and slight increase in fetuses with visceral anomalies in rats. When administered during the period of genital development, there was a dose dependent increase in feminization of male rat fetuses. In a study with a small number of cynomolgous monkeys, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinyl estradiol (100:1) at doses up to 10 mg/kg/day, 11 times the human exposure.

For the AUC of the human dose I used the data from the label giving the highest AUC 0-infinity of 2343. For the animal data I used some of the data from Dr. Raheja's table on pg 4 of the original IND review (rat = 8641, rabbit = 1986 for 10 mg/kg). For the mouse data I used results from a 14 day study which gave an AUC for a 10 mg/kg dose of 893. For the monkey, I averaged two different 10 mg/kg dose AUC's to get 25799. All the data are in the ADME summary, appended.

Conclusion: I agree with Dr. Raheja's opinion that Yasmin should be approved for contraception.

/S/ 4/1/00

Alex Jordan, PhD

NDA 21-098
HFD-580
Jbest/AJordan/KRaheja

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Attachments

The Attachemtns to the report are listed on text pages

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Table or Figure	Page Number

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Figure 1a

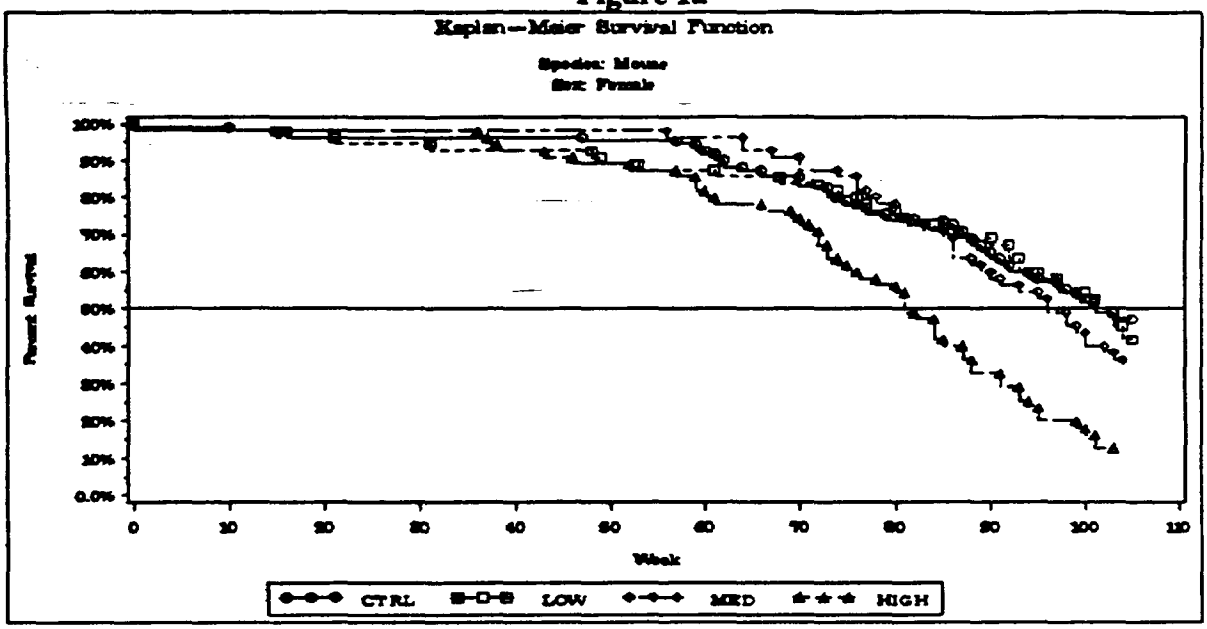

Figure 1b

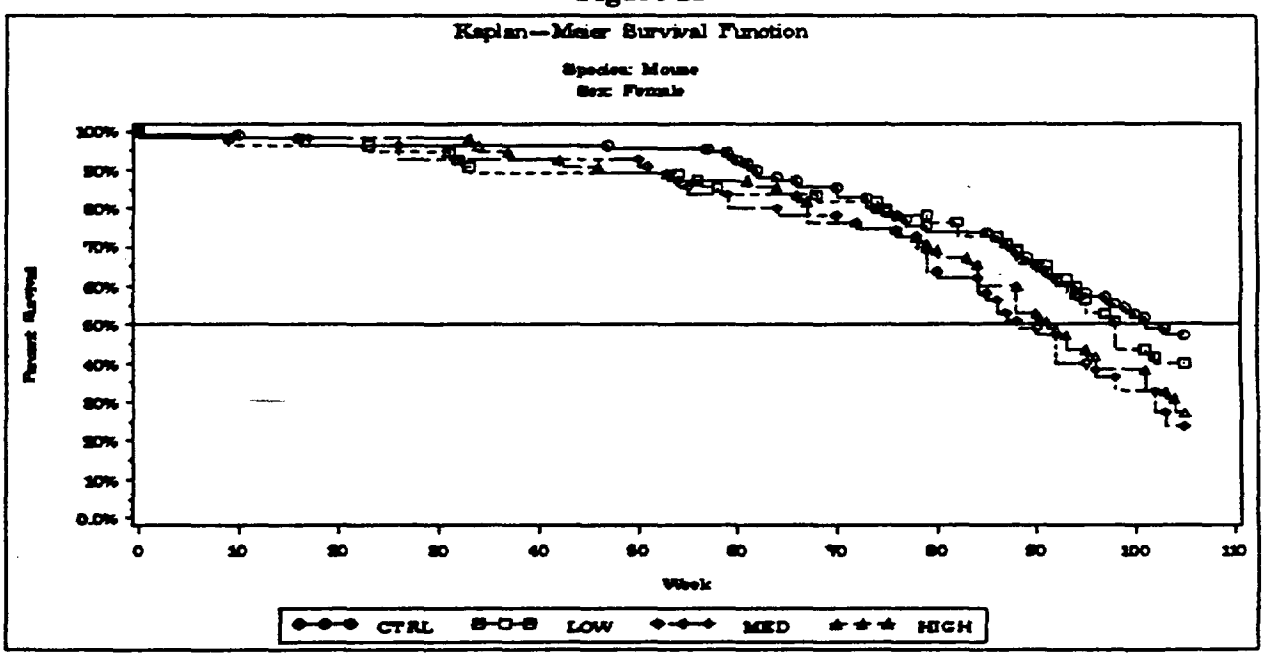

Figure 1c

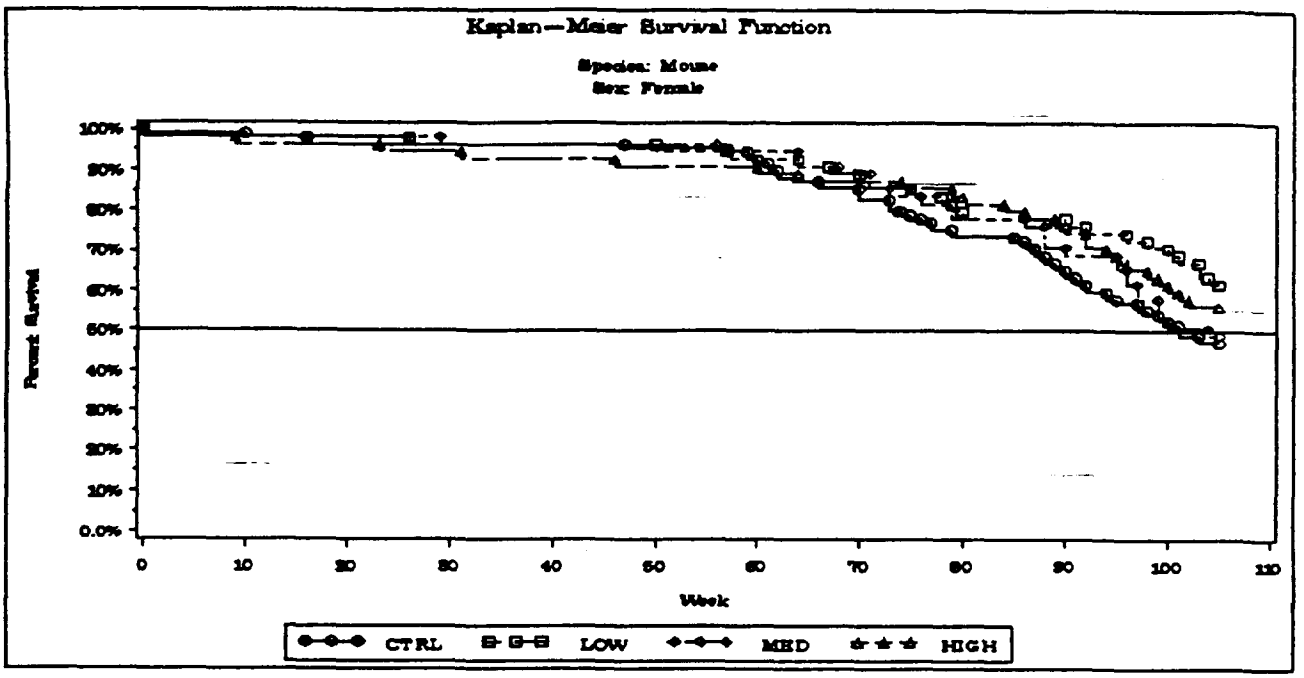

Figure 1d

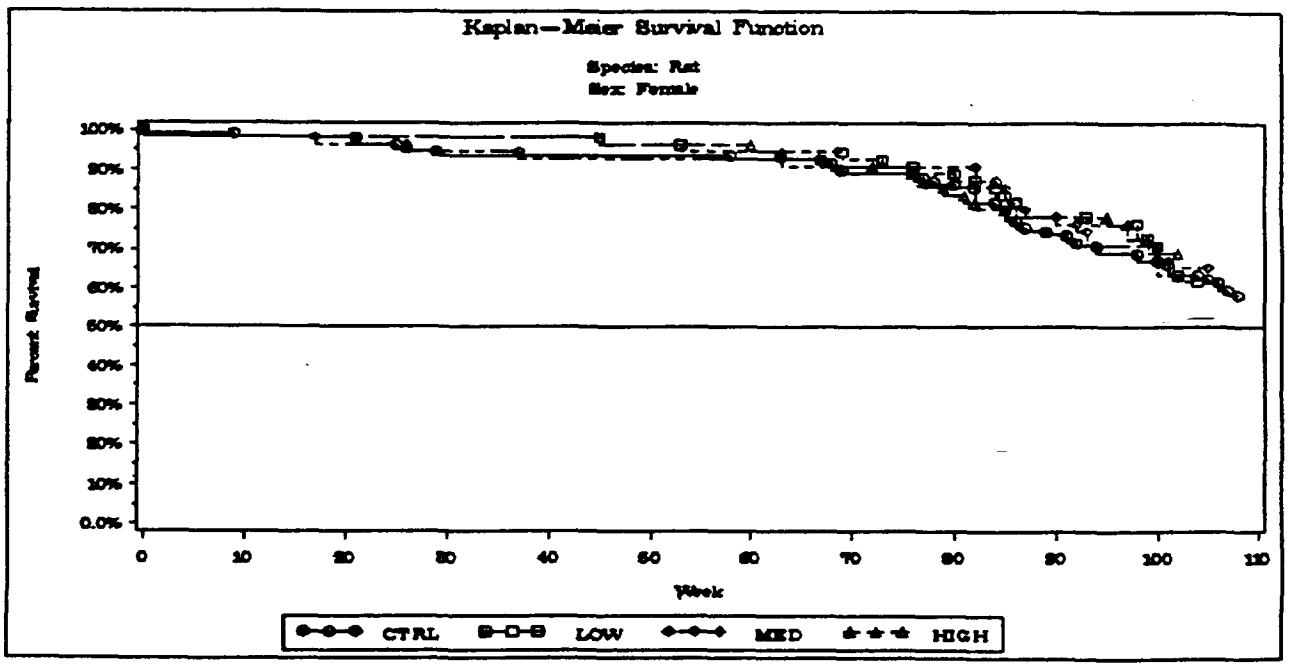

Figure 1e

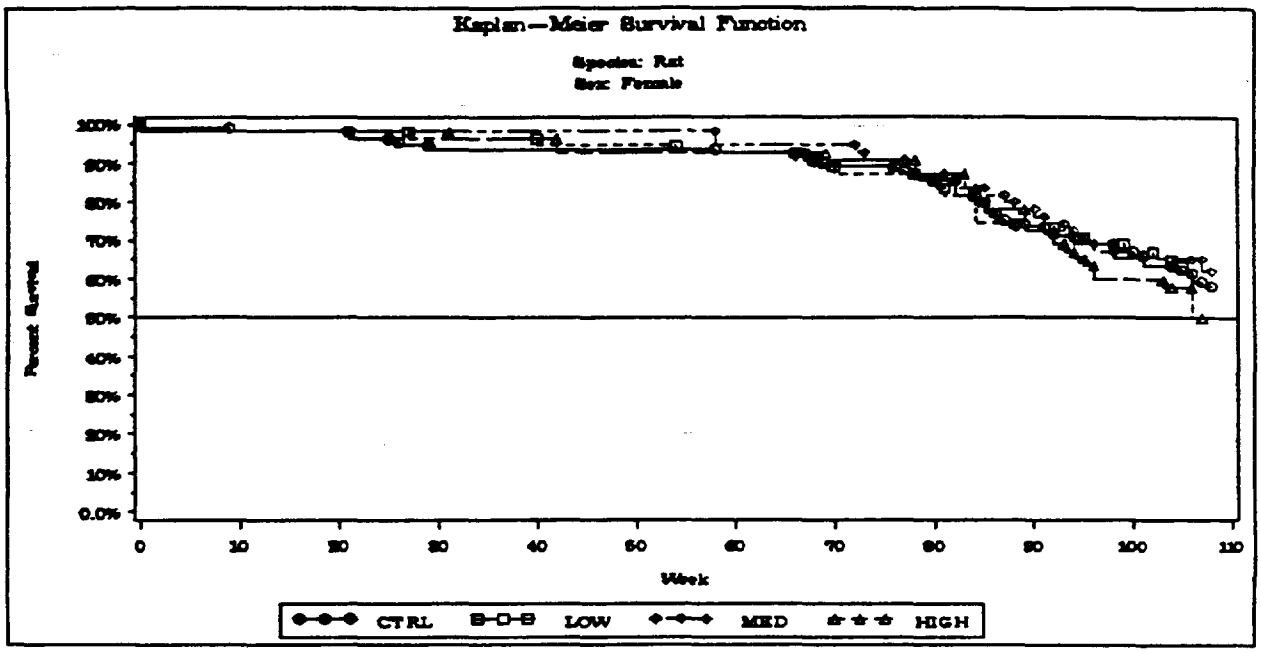

Figure 1f

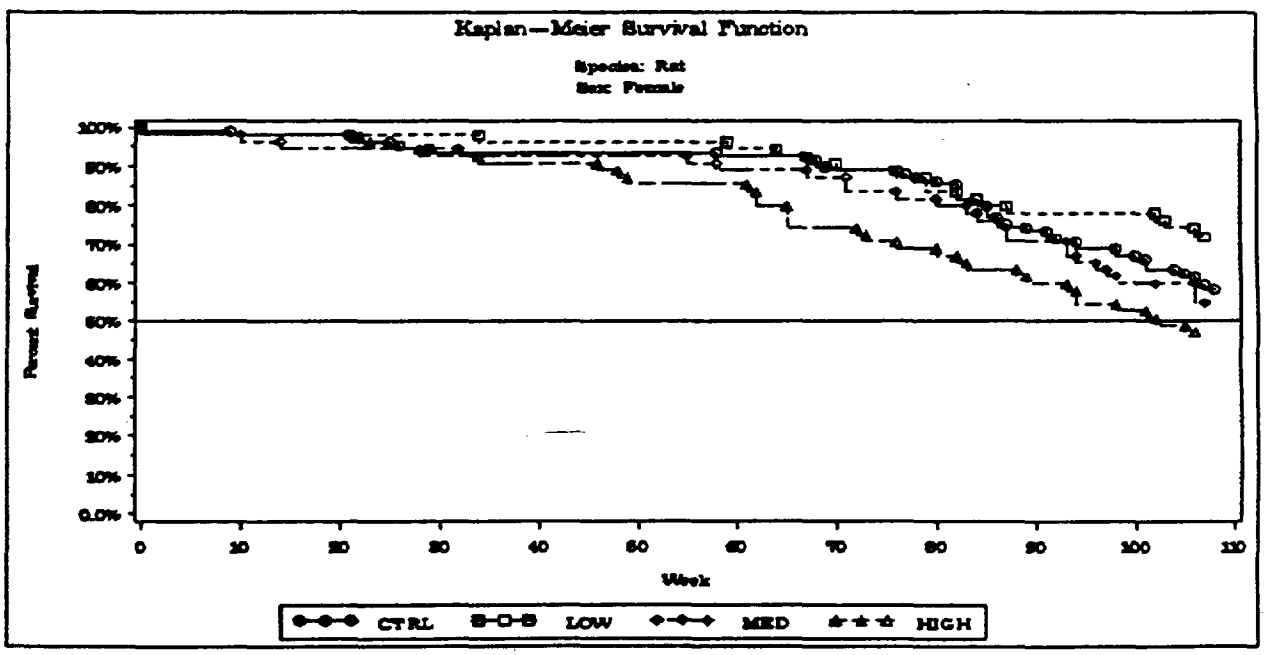

Table 2a

Analysis of Mortality
Species: Mouse
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
Week	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	4	110	3.6	5	55	9.1	5	55	9.1	5	55	9.1
53-78	21	105	22.7	6	50	20.0	10	50	27.3	10	50	27.3
79-81	15	85	36.4	8	44	34.5	13	40	50.9	12	40	48.1
82-106	48	70	80.0	29	36	87.3	26	27	98.2	28	55	50.9
107-107	22	110	20.0	7	55	12.7	1	55	1.8	.	.	.

Table 2b

Analysis of Mortality
Species: Mouse
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
Week	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	4	110	3.6	5	55	9.1	.	.	.	6	55	10.9
53-78	21	105	22.7	7	50	21.8	11	55	20.0	17	49	41.8
79-81	15	85	36.4	6	43	30.9	12	44	41.8	14	32	67.3
82-106	48	70	80.0	30	38	85.5	27	32	90.9	17	18	98.2
107-107	22	110	20.0	8	55	14.5	5	55	9.1	1	55	1.8

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Table 2c

Analysis of Mortality
Species: Mouse
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
Week	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	4	110	3.6	2	55	3.6	1	55	1.8	4	55	7.3
53-78	21	106	22.7	7	53	16.4	8	54	16.4	3	51	12.7
79-91	15	85	36.4	3	46	21.8	7	46	29.1	6	48	23.6
92-106	48	70	80.0	24	43	65.5	27	39	78.2	26	42	70.9
107-107	22	110	20.0	19	55	34.5	12	55	21.8	16	55	29.1

Table 2d

Analysis of Mortality
Species: Rat
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
Week	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	6	110	5.5	1	55	1.8	3	55	5.5	1	55	1.8
53-78	8	104	12.7	4	54	8.1	1	52	7.3	6	54	12.7
79-91	15	96	26.4	5	50	18.2	8	51	21.8	4	48	20.0
92-108	45	81	67.3	36	45	83.6	33	43	81.8	32	44	78.2
109-110	36	110	32.7	9	55	16.4	10	55	18.2	12	55	21.8

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Table 2e

Analysis of Mortality
Species: Rat
Sex: Female

	Dose											
	CTRL			5			6			7		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week												
0-52	6	110	5.5	2	55	3.6	.	.	.	2	55	3.6
53-78	8	104	12.7	5	53	12.7	5	55	9.1	3	53	8.1
79-91	15	96	26.4	7	48	25.5	8	50	23.6	7	50	21.8
92-109	70	81	90.0	39	41	96.4	40	42	96.4	42	43	98.2
110-110	11	110	10.0	2	55	3.6	2	55	3.6	1	55	1.8

Table 2f

Analysis of Mortality
Species: Rat
Sex: Female

	Dose											
	CTRL			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week												
0-52	6	110	5.5	1	55	1.8	3	55	5.5	7	55	12.7
53-78	8	104	12.7	5	54	10.9	6	52	16.4	9	48	29.1
79-91	15	96	26.4	5	49	20.0	5	46	25.5	5	39	38.2
92-109	70	81	90.0	40	44	92.7	38	41	96.4	33	34	98.2
110-110	11	110	10.0	4	55	7.3	2	55	3.6	1	55	1.8

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Table 3a

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	5.29	0.0215
	Depart from Trend	5.39	0.0674
	Homogeneity	10.68	0.0136
Kruskal-Wallis	Dose-Mortality Trend	4.01	0.0453
	Depart from Trend	4.59	0.1007
	Homogeneity	8.60	0.0351

Table 3b

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	28.16	0.0000
	Depart from Trend	0.86	0.6511
	Homogeneity	30.02	0.0000
Kruskal-Wallis	Dose-Mortality Trend	25.84	0.0000
	Depart from Trend	1.34	0.5105
	Homogeneity	25.88	0.0000

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Table 3c

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.61	0.4362
	Depart from Trend	3.43	0.1801
	Homogeneity	4.03	0.2577
Kruskal-Wallis	Dose-Mortality Trend	0.69	0.4068
	Depart from Trend	3.48	0.1759
	Homogeneity	4.16	0.2443

Table 3d

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.65	0.4218
	Depart from Trend	0.05	0.8767
	Homogeneity	0.69	0.8751
Kruskal-Wallis	Dose-Mortality Trend	0.52	0.4730
	Depart from Trend	0.12	0.9411
	Homogeneity	0.64	0.8880

Table 3e

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.22	0.6424
	Depart from Trend	0.30	0.8602
	Homogeneity	0.52	0.9152
Kruskal-Wallis	Dose-Mortality Trend	0.08	0.7678
	Depart from Trend	0.34	0.8434
	Homogeneity	0.43	0.8343

Table 3f

Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	7.02	0.0081
	Depart from Trend	2.45	0.2943
	Homogeneity	9.47	0.0237
Kruskal-Wallis	Dose-Mortality Trend	7.63	0.0057
	Depart from Trend	2.04	0.3615
	Homogeneity	9.66	0.0216

Table 4a

Statistical Interpretation of Significance in Evaluation of Tumor -Data Analyses Currently Adopted by CDER Divisions of Biometrics

* Exact Test - The statistical interpretation of significance is based on the exact test, if one of the two following situation applies.

  1. The tumor is found either fatal to all the animals or non-fatal to all the animals.
  2. The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap.

  The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.

* Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.

* Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overal type-I error at the level of about 10%, this rule states:

  1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.
  2. Otherwise, the 0.005 significance level may be used.

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Table 4a

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No.
Run Date & Time: September 24, 1999 (9:51)
Source:

Note: Dose Levels Included: CTRL LOW MED HIGH (0 1.01 3.03 10.1)
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 / 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
ADRENAL CTX L&R	(AD)	IN	79-91	1	1 0 0 0	1.000	0.816	0.847
	(000)	IN	79-91	2	13 8 13 12			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			
ADRENAL CTX L&R	(AD)	IN	92-106	1	0 0 1 0	0.412	0.495	0.546
PHAEOCHROMOCYTOMA	(914)	IN	92-106	2	48 29 25 28			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 1 0			
ADRENAL MED L&R	(AM)	IN	79-91	1	1 0 0 1	0.425	0.278	0.310
	(000)	IN	79-91	2	13 8 13 10			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 1			
ADRENAL MED L&R	(AM)	IN	92-106	1	0 0 1 0	0.412	0.495	0.546
PHAEOCHROMOCYTOMA	(883)	IN	92-106	2	48 29 25 28			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 1 0			
ADRENAL MED L&R	(AM)	IN	53-78	1	1 0 0 0	1.000	0.772	0.809
PHAEOCHROMOCYTOMA	(953)	IN	53-78	2	20 6 10 10			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			
AORTA	(AO)	IN	53-78	1	1 1 1 1	0.080	0.066	0.072
	(000)	IN	53-78	2	19 4 8 8			
		IN	79-91	1	0 0 2 2			
		IN	79-91	2	15 8 9 8			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 1 3 3			
CAECUM	(CA)	IN	92-106	1	0 1 0 0	0.633	0.695	0.738
ADENOCARCINOMA	(867)	IN	92-106	2	48 28 26 28			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 1 0 0			
COLON	(CO)	IN	92-106	1	0 0 1 0	0.115	0.085	0.100
ADENOCARCINOMA	(546)	IN	92-106	2	48 29 25 28			
		FA	88	1	0 0 0 1			
		FA	88	2	78 39 29 35			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 1 1			
GALL BLADDER	(GB)	IN	0-52	1	0 0 0 1	0.404	0.407	0.422
	(000)	IN	0-52	2	4 5 5 3			
		IN	53-78	1	1 1 0 1			
		IN	53-78	2	19 4 10 8			
		IN	79-91	1	1 1 3 0			
		IN	79-91	2	13 6 7 12			
		IN	92-106	1	1 1 0 1			

		IN 92-106	2	46	27	26	26		
Spontaneous tumor pct: 3%	in ctrl. - Total	-		3	3	3	3		
HARDERIAN GLANDS	(HG)	IN 92-106	1	0	0	0	1	0.213	0.032	0.043
CARCINOMA	(127)	IN 92-106	2	48	29	26	27		
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-		0	0	0	1		
HARDERIAN GLANDS	(HG)	IN 53-78	1	1	0	0	0	0.706	0.706	0.720
ADENOMA	(203)	IN 53-78	2	20	6	10	10		
		IN 79-91	1	1	1	0	0		
		IN 79-91	2	14	7	13	12		
		IN 92-106	1	3	1	1	2		
		IN 92-106	2	45	28	25	26		
		IN 107-107	1	3	0	0	0		
		IN 107-107	2	19	7	1	0		
Spontaneous tumor pct: 7%	in ctrl. - Total	-		8	2	1	2		
H'POIETIC TUMOUR	(HP)	IN 53-78	1	1	0	0	0	0.900	0.893	0.897
MALIGNANT LYMPHOMA	(052)	IN 53-78	2	13	4	9	9		
		IN 92-106	1	4	3	0	2		
		IN 92-106	2	42	23	24	26		
		IN 107-107	1	7	1	0	0		
		IN 107-107	2	15	6	1	0		
		FA 23	1	0	1	0	0		
		FA 23	2	108	53	54	55		
		FA 34	1	0	0	0	1		
		FA 34	2	108	50	53	53		
		FA 50	1	0	0	1	0		
		FA 50	2	106	50	52	50		
		FA 56	1	0	1	0	0		
		FA 56	2	106	48	47	49		
		FA 59	1	1	0	0	0		
		FA 59	2	104	47	47	49		
		FA 61	1	1	0	0	0		
		FA 61	2	101	47	46	49		
		FA 64	1	0	0	1	1		
		FA 64	2	99	47	45	47		
		FA 70	1	1	0	0	0		
		FA 70	2	95	46	44	45		
		FA 73	1	1	0	0	0		
		FA 73	2	93	46	42	42		
		FA 74	1	2	0	0	0		
		FA 74	2	89	46	42	42		
		FA 75	1	0	1	0	0		
		FA 75	2	88	44	42	42		
		FA 76	1	1	0	0	0		
		FA 76	2	86	44	42	42		
		FA 79	1	0	1	0	0		
		FA 79	2	85	43	40	40		
		FA 85	1	1	0	1	0		
		FA 85	2	82	42	33	36		
		FA 87	1	1	0	0	0		
		FA 87	2	79	40	31	36		
		FA 88	1	0	0	0	1		
		FA 88	2	78	39	29	35		
		FA 91	1	1	0	0	0		
		FA 91	2	71	38	27	29		
		FA 92	1	1	0	1	0		

			FA 92	2	69	36	26	28		
			FA 93	1	0	1	0	0		
			FA 93	2	68	35	26	27		
			FA 97	1	0	1	0	0		
			FA 97	2	64	30	21	23		
			FA 101	1	1	1	0	0		
			FA 101	2	57	27	20	23		
			FA 105	1	0	0	1	0		
			FA 105	2	54	23	14	17		
Spontaneous tumor pct: 22%		in ctrl. -	Total	-	24	11	5	5		
H'POIETIC TUMOUR	(HP	)	IN 92-106	1	1	0	0	0	0.246	0.241 0.255
HISTIOCYTIC SARCOMA	(299	)	IN 92-106	2	46	28	26	26		
			IN 107-107	1	1	0	0	0		
			IN 107-107	2	21	7	1	0		
			FA 60	1	1	0	0	0		
			FA 60	2	103	47	46	49		
			FA 66	1	0	0	0	1		
			FA 66	2	97	47	44	46		
			FA 79	1	1	0	0	0		
			FA 79	2	84	44	40	40		
			FA 89	1	1	0	0	0		
			FA 89	2	75	38	28	33		
			FA 95	1	0	0	0	1		
			FA 95	2	66	32	26	25		
			FA 100	1	1	0	0	0		
			FA 100	2	59	28	20	23		
			FA 105	1	0	1	0	1		
			FA 105	2	54	22	15	16		
Spontaneous tumor pct: 5%		in ctrl. -	Total	-	6	1	0	3		
H'POIETIC TUMOUR	(HP	)	IN 92-106	1	0	0	0	1	0.213	0.032 0.043
PLASMA CELL LYMPHOMA	(347	)	IN 92-106	2	48	29	26	27		
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	0	0	0	1		
ILEUM	(IL	)	IN 0-52	1	0	0	0	1	0.072	0.034 0.041
	(000	)	IN 0-52	2	4	5	5	3		
			IN 92-106	1	0	1	0	1		
			IN 92-106	2	48	27	26	26		
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	0	1	0	2		
JEJUNUM	(JE	)	IN 53-78	1	1	0	0	0	1.000	0.776 0.812
	(000	)	IN 53-78	2	19	6	10	10		
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	1	0	0	0		
L N	(LC	)	IN 53-78	1	1	0	1	0	0.365	0.384 0.409
	(000	)	IN 53-78	2	19	6	8	10		
			IN 92-106	1	0	1	0	1		
			IN 92-106	2	48	27	26	26		
Spontaneous tumor pct: <= 1%		in ctrl. -	Total	-	1	1	1	1		
LACHRYMAL GLANDS	(LG	)	IN 53-78	1	1	0	0	0	1.000	0.799 0.832
	(000	)	IN 53-78	2	19	6	10	10		
			IN 107-107	1	1	0	0	0		
			IN 107-107	2	20	7	1	0		
Spontaneous tumor pct: 2%		in ctrl. -	Total	-	2	0	0	0		
LIVER X 2	(LIO	)	IN 79-91	1	0	0	0	1	0.251	0.202 0.229

HEPATOCELLULAR ADENOMA	(609)	IN 79-91	2	15	8	13	11			
		IN 92-106	1	0	1	0	0			
		IN 92-106	2	48	28	26	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	1	0	1			
LIVER X 2	(LIO)	IN 92-106	1	0	1	0	0	0.633	0.695	0.738
HAEMANGIOMA	(730)	IN 92-106	2	48	28	26	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	1	0	0			
LIVER X 2	(LIO)	IN 92-106	1	0	0	1	1	0.129	0.094	0.110
HEPATOCELLULAR CARCINOMA	(789)	IN 92-106	2	48	29	25	27			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	0	1	1			
LIVER X 2	(LIO)	IN 92-106	1	1	0	1	0	0.656	0.705	0.736
HAEMANGIOSARCOMA	(933)	IN 92-106	2	47	29	25	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		1	0	1	0			
LUNGS X 2	(LLO)	IN 53-78	1	0	1	0	1	0.887	0.879	0.885
PULMONARY ADENOMA	(091)	IN 53-78	2	21	5	10	9			
		IN 79-91	1	2	1	0	0			
		IN 79-91	2	13	7	13	12			
		IN 92-106	1	6	5	1	2			
		IN 92-106	2	42	24	25	26			
		IN 107-107	1	4	0	0	0			
		IN 107-107	2	18	7	1	0			
Spontaneous tumor pct: 11% in ctrl. - Total		-		12	7	1	3			
LUNGS X 2	(LLO)	IN 53-78	1	1	0	0	0	0.518	0.522	0.539
PULMONARY CARCINOMA	(290)	IN 53-78	2	20	6	10	10			
		IN 79-91	1	0	0	0	1			
		IN 79-91	2	14	7	13	11			
		IN 92-106	1	0	2	1	1			
		IN 92-106	2	47	27	25	27			
		IN 107-107	1	2	0	0	0			
		IN 107-107	2	20	7	1	0			
		FA 88	1	0	1	0	0			
		FA 88	2	78	38	29	36			
		FA 91	1	1	0	0	0			
		FA 91	2	71	38	27	29			
		FA 94	1	1	0	0	0			
		FA 94	2	67	34	26	26			
Spontaneous tumor pct: 5% in ctrl. - Total		-		5	3	1	2			
L N	(LM)	IN 53-78	1	1	0	0	0	1.000	0.861	0.880
	(000)	IN 53-78	2	19	6	10	10			
		IN 92-106	1	1	0	0	0			
		IN 92-106	2	46	29	26	28			
Spontaneous tumor pct: 2% in ctrl. - Total		-		2	0	0	0			
L N	(LS)	IN 79-91	1	0	0	1	0	0.056	0.046	0.056
	(000)	IN 79-91	2	15	8	11	12			
		IN 92-106	1	0	0	0	1			
		IN 92-106	2	48	29	26	26			
		IN 107-107	1	0	0	1	0			
		IN 107-107	2	22	7	-1	0			
Spontaneous tumor pct: <= 1% in ctrl. - Total		-		0	0	2	1			
L N	(LT)	IN 79-91	1	0	0	1	0	0.510	0.549	0.597

	(000)	IN	79-91	2	15	8	11	12		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0		
MAMMARY A. CA/CR	(MA)	IN	53-78	1	1	0	0	0	0.249	0.245 0.258
CARCINOMA	(429)	IN	53-78	2	20	6	9	10		
		IN	79-91	1	0	0	0	2		
		IN	79-91	2	15	6	10	10		
		IN	92-106	1	0	1	0	0		
		IN	92-106	2	48	28	26	28		
		IN	107-107	1	1	0	1	0		
		IN	107-107	2	21	7	0	0		
		FA	72	1	0	0	1	0		
		FA	72	2	94	46	42	45		
		FA	80	1	0	0	1	0		
		FA	80	2	83	43	37	39		
		FA	85	1	0	0	1	0		
		FA	85	2	83	42	33	36		
		FA	86	1	0	2	0	0		
		FA	86	2	81	40	32	36		
		FA	87	1	0	0	1	0		
		FA	87	2	80	40	30	36		
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	3	5	2		
MAMMARY A. CA/CR	(MA)	IN	53-78	1	0	0	1	1	0.207	0.192 0.205
ADENOACANTHOMA	(531)	IN	53-78	2	21	6	9	9		
		IN	79-91	1	0	0	1	0		
		IN	79-91	2	15	8	12	12		
		IN	92-106	1	0	2	0	0		
		IN	92-106	2	48	26	25	27		
		IN	107-107	1	1	0	0	0		
		IN	107-107	2	21	7	1	0		
		FA	95	1	0	0	1	0		
		FA	95	2	66	32	25	26		
		FA	96	1	0	0	0	1		
		FA	96	2	64	31	22	23		
		FA	101	1	0	1	0	0		
		FA	101	2	58	27	20	23		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	3	3	2		
MAMMARY A. CA/CR	(MA)	IN	79-91	1	0	0	1	0	0.557	0.671 0.703
ADENOMA	(659)	IN	79-91	2	15	8	12	12		
		IN	92-106	1	0	1	0	0		
		IN	92-106	2	48	28	26	28		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	1	0		
MAMMARY A. CA/CR	(MA)	IN	92-106	1	0	0	1	0	0.382	0.452 0.489
CARCINOSARCOMA	(844)	IN	92-106	2	48	29	24	28		
		FA	102	1	0	0	1	0		
		FA	102	2	57	24	19	21		
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	2	0		
MUSCULO-SKELETAL	(MS)	IN	92-106	1	0	0	0	1	0.052	0.040 0.047
OSTEOSARCOMA	(374)	IN	92-106	2	48	29	26	27		
		FA	54	1	0	0	1	0		
		FA	54	2	106	50	48	49		
		FA	74	1	0	1	0	0		
		FA	74	2	91	45	42	42		
		FA	90	1	0	0	0	1		

		FA 90	2	74	38	28	32			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	2			
MUSCULO-SKELETAL	(MS)	IN 79-91	1	0	0	0	1	0.250	0.048	0.062
OSTEOMA	(622)	IN 79-91	2	15	8	13	11			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1			
MESENTERY	(MT)	IN 53-78	1	1	0	0	0	1.000	0.776	0.812
	(000)	IN 53-78	2	19	6	10	10			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0			
MESENTERY	(MT)	IN 92-106	1	0	1	0	0	0.633	0.695	0.738
MESOTHELIOMA	(550)	IN 92-106	2	48	28	26	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0			
OVARIES+OVIDUCTS	(OA)	IN 53-78	1	1	0	0	0	0.877	0.851	0.867
	(000)	IN 53-78	2	19	6	10	10			
		IN 79-91	1	1	0	1	0			
		IN 79-91	2	13	8	11	12			
Spontaneous tumor pct: 2% in ctrl. - Total			-	2	0	1	0			
OVARIES+OVIDUCTS	(OA)	IN 53-78	1	1	0	0	0	0.982	0.929	0.938
ADENOMA	(725)	IN 53-78	2	19	6	10	10			
		IN 79-91	1	1	0	0	0			
		IN 79-91	2	13	8	12	12			
		IN 92-106	1	1	1	0	0			
		IN 92-106	2	47	28	26	28			
Spontaneous tumor pct: 3% in ctrl. - Total			-	3	1	0	0			
OVARIES+OVIDUCTS	(OA)	IN 92-106	1	1	0	1	1	0.307	0.282	0.308
GRANULOSA/THECA CELL TUMO	(837)	IN 92-106	2	47	29	25	27			
		IN 107-107	1	1	0	0	0			
		IN 107-107	2	21	7	1	0			
Spontaneous tumor pct: 2% in ctrl. - Total			-	2	0	1	1			
OVARIES+OVIDUCTS	(OA)	IN 92-106	1	2	0	0	0	1.000	0.874	0.892
LUTEOMA	(938)	IN 92-106	2	46	29	26	28			
		IN 107-107	1	1	0	0	0			
		IN 107-107	2	21	7	1	0			
Spontaneous tumor pct: 3% in ctrl. - Total			-	3	0	0	0			
OESOPHAGUS	(OE)	IN 79-91	1	0	0	1	0	0.510	0.549	0.597
	(000)	IN 79-91	2	15	8	11	12			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0			
OESOPHAGUS	(OE)	FA 88	1	0	0	0	1	0.197	0.026	0.035
SQUAMOUS CELL CARCINOMA	(544)	FA 88	2	78	39	29	35			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1			
OPTIC NERVES L&R	(OP)	IN 92-106	1	1	0	0	0	1.000	0.803	0.836
	(000)	IN 92-106	2	46	29	26	28			
		IN 107-107	1	1	0	0	0			
		IN 107-107	2	20	7	1	0			
Spontaneous tumor pct: 2% in ctrl. - Total			-	2	0	0	0			
PANCREAS	(PA)	IN 53-78	1	1	0	0	0	1.000	0.776	0.812
	(000)	IN 53-78	2	19	6	10	10			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0			

PANCREAS	(PA)	IN	92-106	1	0	0	1	0	0.412 0.495 0.546
ISLET CELL ADENOMA	(503)	IN	92-106	2	48	29	25	28	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	0	1	0	
PARATHYROIDS	(PD)	IN	0-52	1	1	1	2	0	0.077 0.072 0.075
	(000)	IN	0-52	2	2	3	1	5	
		IN	53-78	1	8	2	3	2	
		IN	53-78	2	5	2	4	6	
		IN	79-91	1	3	0	1	5	
		IN	79-91	2	9	8	11	2	
		IN	92-106	1	7	5	8	8	
		IN	92-106	2	34	19	10	12	
		IN	107-107	1	2	1	1	0	
		IN	107-107	2	18	5	-1	0	
Spontaneous tumor pct: 19% in ctrl. - Total		-			21	9	15	15	
PITUITARY	(PI)	IN	53-78	1	0	0	0	4	0.000 0.000 0.000
ADENOMA	(121)	IN	53-78	2	21	6	9	6	
		IN	79-91	1	0	1	2	0	
		IN	79-91	2	15	7	9	5	
		IN	92-106	1	1	6	6	8	
		IN	92-106	2	46	21	19	16	
		IN	107-107	1	2	2	1	0	
		IN	107-107	2	20	5	0	0	
		FA	70	1	0	0	1	0	
		FA	70	2	96	46	43	45	
		FA	79	1	0	0	0	1	
		FA	79	2	85	44	40	39	
		FA	80	1	0	0	0	1	
		FA	80	2	83	43	38	38	
		FA	83	1	0	0	0	1	
		FA	83	2	83	42	35	37	
		FA	86	1	0	0	1	0	
		FA	86	2	81	42	31	36	
		FA	87	1	0	0	1	0	
		FA	87	2	80	40	30	36	
		FA	88	1	0	0	0	1	
		FA	88	2	78	39	29	35	
		FA	90	1	0	0	0	3	
		FA	90	2	74	38	28	30	
		FA	101	1	0	1	0	1	
		FA	101	2	58	27	20	22	
		FA	102	1	0	1	0	0	
		FA	102	2	57	23	20	21	
		FA	103	1	0	0	1	2	
		FA	103	2	57	23	17	19	
		FA	105	1	1	0	0	1	
		FA	105	2	53	23	15	16	
Spontaneous tumor pct: 4% in ctrl. - Total		-			4	11	13	23	(Asymptotic P<0.005)
PITUITARY	(PI)	FA	64	1	0	0	1	0	0.459 0.416 0.446
CARCINOMA	(272)	FA	64	2	99	47	45	48	
		FA	79	1	0	0	1	0	
		FA	79	2	85	44	39	40	
		FA	105	1	0	0	1	0	
		FA	105	2	54	23	14	17	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-			0	0	3	0	

PITUITARY	(PI |)	IN	107-107	1	1	0	0	0	1.000	0.696	0.898
ADENOMA OF PARS INTERMEDI	(888	)	IN	107-107	2	21	7	1	0			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1	0	0	0			
PITUITARY	(PI |)	IN	53-78	1	1	0	0	0	1.000	0.772	0.809
CRANIOPHARYNGIOMA	(912	)	IN	53-78	2	20	6	10	10			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1	0	0	0			
PERITONEUM	(PT |)	IN	92-106	1	0	1	0	0	0.633	0.695	0.738
MESOTHELIOMA	(928	)	IN	92-106	2	48	28	26	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	1	0	0			
SALIVARY GLANDS	(SA |)	IN	53-78	1	1	0	0	0	1.000	0.776	0.812
	(000	)	IN	53-78	2	19	6	10	10			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1	0	0	0			
SPINAL C.CERV	(SCO |)	IN	0-52	1	1	0	0	0	1.000	0.838	0.867
	(000	)	IN	0-52	2	2	5	5	5			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1	0	0	0			
SKIN OTHER	(SKO |)	FA	31	1	0	1	0	0	0.198	0.154	0.177
SQUAMOUS CELL CARCINOMA	(043	)	FA	31	2	108	52	53	55			
			FA	76	1	0	0	0	1			
			FA	76	2	87	44	42	41			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	1	0	1			
SKIN OTHER	(SKO |)	IN	79-91	1	0	0	1	0	0.459	0.438	0.464
SARCOMA	(162	)	IN	79-91	2	15	8	12	12			
			IN	92-106	1	1	0	0	0			
			IN	92-106	2	47	29	26	28			
			FA	72	1	0	0	0	1			
			FA	72	2	94	46	43	44			
			FA	73	1	1	0	0	0			
			FA	73	2	93	46	42	42			
Spontaneous tumor pct: 2% in ctrl. - Total					-	2	0	1	1			
SKIN OTHER	(SKO |)	FA	78	1	0	0	0	1	0.194	0.025	0.034
MIXED SALIVARY GLAND TUMO	(241	)	FA	78	2	85	44	41	40			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	0	1			
SKIN OTHER	(SKO |)	FA	88	1	0	0	1	0	0.357	0.465	0.517
SEBACEOUS ADENOMA	(458	)	FA	88	2	78	39	28	36			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0			
STERNUM & MARROW	(SN |)	IN	92-106	1	0	0	0	1	0.207	0.030	0.040
	(000	)	IN	92-106	2	48	29	26	26			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	0	1			
SPLEEN	(SP |)	IN	92-106	1	0	0	1	0	0.412	0.495	0.546
HAEMANGIOMA	(878	)	IN	92-106	2	48	29	25	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0	0	1	0			
TRACHEA	(TR |)	IN	53-78	1	1	0	0	0	1.000	0.776	0.812
	(000	)	IN	53-78	2	19	6	10	10			
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1	0	0	0			
THYMUS	(TY |)	IN	79-91	1	1	0	1	0	0.468	0.495	0.518

	(000)	IN	79-91	2	13	8	11	12		
		IN	92-106	1	1	0	1	1		
		IN	92-106	2	46	29	24	26		
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	2	0	2	1		
URINARY BLADDER	(UB)	IN	92-106	1	2	0	0	0	1.000	0.866 0.885
	(000)	IN	92-106	2	44	29	26	28		
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	2	0	0	0		
UTERUS	(UT)	IN	53-78	1	0	0	1	1	0.799	0.796 0.802
STROMAL POLYP	(085)	IN	53-78	2	21	6	8	9		
		IN	79-91	1	2	1	2	2		
		IN	79-91	2	12	7	9	10		
		IN	92-106	1	8	11	4	3		
		IN	92-106	2	39	18	22	25		
		IN	107-107	1	2	1	0	0		
		IN	107-107	2	20	6	1	0		
		FA	50	1	0	0	1	0		
		FA	50	2	106	50	52	50		
		FA	59	1	0	0	1	0		
		FA	59	2	105	47	46	49		
		FA	79	1	0	0	1	0		
		FA	79	2	85	44	39	40		
		FA	80	1	0	0	1	0		
		FA	80	2	83	43	37	39		
		FA	90	1	1	0	0	0		
		FA	90	2	73	38	28	33		
		FA	105	1	1	0	0	0		
		FA	105	2	53	23	15	17		
Spontaneous tumor pct: 13%	in ctrl. -	Total		-	14	13	11	6		
UTERUS	(UT)	IN	53-78	1	1	0	0	0	1.000	0.858 0.878
HAEMANGIOMA	(116)	IN	53-78	2	20	6	10	10		
		IN	92-106	1	1	0	0	0		
		IN	92-106	2	47	29	26	28		
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	2	0	0	0		
UTERUS	(UT)	IN	79-91	1	0	1	0	0	0.839	0.850 0.864
LEIOMYOMA	(292)	IN	79-91	2	15	7	13	12		
		IN	92-106	1	1	1	1	0		
		IN	92-106	2	47	28	25	28		
		IN	107-107	1	2	0	0	0		
		IN	107-107	2	20	7	1	0		
Spontaneous tumor pct: 3%	in ctrl. -	Total		-	3	2	1	0		
UTERUS	(UT)	IN	79-91	1	0	0	0	1	0.091	0.071 0.077
LEIOMYOSARCOMA	(368)	IN	79-91	2	13	8	12	11		
		IN	92-106	1	2	0	0	3		
		IN	92-106	2	46	29	26	25		
		FA	80	1	0	0	1	0		
		FA	80	2	83	43	37	39		
		FA	86	1	1	0	0	0		
		FA	86	2	80	42	32	36		
		FA	88	1	1	0	0	0		
		FA	88	2	77	39	29	36		
Spontaneous tumor pct: 4%	in ctrl. -	Total		-	4	0	1	4		
UTERUS	(UT)	IN	92-106	1	0	0	5	2	0.091	0.083 0.090

ADENOCARCINOMA	(435)	IN	92-106	2	48	29	21	26			
		FA	79	1	0	0	1	0			
		FA	79	2	85	44	39	40			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	6	2			
UTERUS	(UT)	IN	92-106	1	1	0	0	0	0.961	0.879	0.893
HAEMANGIOSARCOMA	(646)	IN	92-106	2	47	28	26	28			
		IN	107-107	1	2	0	0	0			
		IN	107-107	2	20	7	1	0			
		FA	85	1	1	0	0	0			
		FA	85	2	82	42	34	36			
		FA	98	1	0	1	0	0			
		FA	98	2	63	28	21	23			
Spontaneous tumor pct: 4% in ctrl. - Total				-	4	1	0	0			
UTERUS	(UT)	IN	92-106	1	1	0	0	0	1.000	0.779	0.816
GRANULAR CELL TUMOUR	(823)	IN	92-106	2	47	29	26	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0			
UTERINE CERVIX	(UX)	IN	53-78	1	0	0	1	0	0.731	0.778	0.796
	(000)	IN	53-78	2	21	6	8	10			
		IN	92-106	1	2	0	1	0			
		IN	92-106	2	44	29	24	28			
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	0	2	0			
UTERINE CERVIX	(UX)	IN	79-91	1	0	0	0	1	0.250	0.048	0.062
BASAL CELL TUMOUR	(408)	IN	79-91	2	15	8	13	11			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1			
UTERINE CERVIX	(UX)	IN	53-78	1	1	0	0	0	0.347	0.346	0.358
STROMAL POLYP	(543)	IN	53-78	2	20	6	9	10			
		IN	79-91	1	0	1	0	2			
		IN	79-91	2	15	7	12	10			
		IN	92-106	1	2	4	0	2			
		IN	92-106	2	43	25	25	26			
		FA	50	1	0	0	1	0			
		FA	50	2	104	50	50	50			
		FA	80	1	0	0	1	0			
		FA	80	2	81	43	36	39			
		FA	105	1	1	0	0	0			
		FA	105	2	52	23	14	17			
Spontaneous tumor pct: 4% in ctrl. - Total				-	4	5	2	4			
UTERINE CERVIX	(UX)	IN	92-106	1	1	0	0	0	1.000	0.781	0.817
FIBROMA	(778)	IN	92-106	2	45	29	25	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0			
UTERINE CERVIX	(UX)	IN	107-107	1	1	1	0	0	0.469	0.356	0.571
LEIOMYOMA	(824)	IN	107-107	2	21	6	1	0			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	1	0	0			
UTERINE CERVIX	(UX)	IN	53-78	1	0	0	1	0	0.426	0.492	0.528
ADENOCARCINOMA	(919)	IN	53-78	2	21	6	8	10			
		IN	92-106	1	0	0	1	0			
		IN	92-106	2	46	29	24	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	2	0			
VAGINA	(VG)	IN	53-78	1	1	0	1	0	0.811	0.810	0.829

	(000)	IN	53-78	2	19	6	8	10	
		IN	92-106	1	1	0	0	0	
		IN	92-106	2	46	29	26	28	
Spontaneous tumor pct: 2%	in ctrl. -	Total		-	2	0	1	0	
VAGINA	(VG)	IN	79-91	1	0	0	1	0	0.520 0.548 0.597
BASAL CELL ADENOMA	(271)	IN	79-91	2	15	8	12	12	
Spontaneous tumor pct: <= 1%	in ctrl. -	Total		-	0	0	1	0	

Table 4b

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Study No.
Run Date & Time: September 24, 1999 (10:06)
Source: C:\NG\mice2.dat

Note: Dose Levels Included: CTRL LOW MED HIGH (0 0.01 0.03 0.1)
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 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)
ADRENAL CTX L&R	(AD)	IN	79-91	1	1 0 0 0	1.000	0.832	1.000
	(000)	IN	79-91	2	13 5 12 14			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			
ADRENAL CTX L&R	(AD)	IN	107-107	1	0 1 0 0	0.388	0.482	1.000
PHAEOCHROMOCYTOMA	(914)	IN	107-107	2	22 7 5 1			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 1 0 0			
ADRENAL CTX L&R	(AD)	IN	92-106	1	0 0 1 0	0.360	0.416	1.000
CORTICAL ADENOMA	(915)	IN	92-106	2	48 30 26 17			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 1 0			
ADRENAL MED L&R	(AM)	IN	79-91	1	1 0 0 0	1.000	0.832	1.000
	(000)	IN	79-91	2	13 5 12 14			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			
ADRENAL MED L&R	(AM)	IN	53-78	1	1 0 0 0	1.000	0.810	1.000
PHAEOCHROMOCYTOMA	(953)	IN	53-78	2	20 7 11 17			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 0			
AORTA	(AO)	IN	53-78	1	1 0 0 0	0.144	0.066	1.000
	(000)	IN	53-78	2	19 7 11 17			
		IN	79-91	1	0 0 0 1			
		IN	79-91	2	15 5 12 12			
		IN	92-106	1	0 0 0 1			
		IN	92-106	2	48 30 27 15			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1 0 0 2			
CAECUM	(CA)	IN	53-78	1	0 1 0 0	0.618	0.743	1.000
	(000)	IN	53-78	2	21 5 11 17			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 1 0 0			
CLITORAL GLANDS	(CL)	FA	70	1	0 0 1 0	0.394	0.458	1.000
CARCINOMA	(372)	FA	70	2	96 47 50 42			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 0 1 0			
COLON	(CO)	IN	0-52	1	0 1 0 0	0.714	0.775	1.000
	(000)	IN	0-52	2	4 3 0 6			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0 1 0 0			
DUODENUM	(DU)	IN	0-52	1	0 1 0 0	0.081	0.075	1.000
	(000)	IN	0-52	2	4 3 0 6			