CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

CHEMISTRY REVIEW(S)

JUL 7 1997

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-632 **DATE REVIEWED:** 7-July-97

CHEMISTRY REVIEW #: 4 **REVIEWER:** Martin Haber, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	7-AUG-95	9-AUG-95	16-AUG-95
AMENDMENT	3-JAN-97	6-JAN-97	
AMENDMENT	29-JAN-97	30-JAN-97	

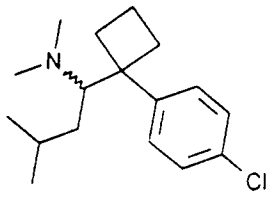
NAME & ADDRESS OF SPONSOR: Knoll Pharmaceutical Company
3000 Continental Drive, North
Mount Olive, NJ 07828-1234 (201) 331-7561

DRUG PRODUCT NAME:

Proprietary:	Meridia
Nonproprietary:	Sibutramine hydrochloride monohydrate
Code Name/#:	BTS 54 524
Chem.Type/Therapeutic.Class:	Type 1, NME/ Class S

PHARMACOL. CATEGORY/INDICATION: Treatment of obesity
DOSAGE FORM: Capsules
STRENGTHS: 5, 10, 15 and 20 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: __X__ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(±)-Cyclobutanemethanamine,1-(4-chlorophenyl)-*N,N*-dimethyl -α-(2-methylpropyl)-,hydrochloride, monohydrate; *N*-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}-*N,N*-dimethylamine hydrochloride monohydrate

CAS #: 125494-59-9, $C_{17}H_{29}Cl_2NO$, mol. wt. 334.33

REMARKS:

The 1/3/97 amendment provides for revised impurity specifications for the drug product. The related substance specification has been revised as follows:

The 1/29/97 amendment provides for updated package insert labeling. Previous chemistry reviews are dated as follows: #1, 10/10/96; #2, 10/28/96 and #3, 11/4/96.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry viewpoint the information provided is satisfactory and the application can be approved.

Orig. NDA # 20-632
cc: HFD-510/Division file/S.Moore/M.Haber/M.Hess /J.Gibbs/S.Koepke

Martin Haber, Ph.D.
Review Chemist

R/D Init by: Dr. Moore, Team Leader Chemist

7/7/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products

NOV - 6 1996

Memorandum

Date: November 6, 1996

From: Martin Haber, Ph.D., Review Chemist, HFD-510 11/6/96

Through: Stephen Moore, Ph.D., Team Leader Chemist, HFD-510 11/6/96

Subject: Addendum to Chemistry Review #3, dated 11/4/96
Revised Regulatory Specifications and Methods

To: NDA 20-632

The currently proposed regulatory limits for related substances (impurities) in the drug product are not more than , not more than other individual and not more than These limits are being re-evaluated herein. Judging from the actual stability data for clinical and production qualification batches, these limits for impurities have not been approached in practice.

However, lower limits for the other individual degradants (impurities) may be set. A justification for the current limits is not found in the NDA.

Telephone memo of conversations on 11/5/96-11/6/96 with Dr. A. Varghese, Regulatory Affairs Director, Knoll Pharmaceutical Co.: We discussed setting of the regulatory limits for impurities and various proposals to revise these limits were made. Knoll proposes a revised limit of I requested data on individual impurities from batches produced to date.

The following comment concerning CMC issues should be communicated to the sponsor:

> Because several individual impurities/degradants in the drug product have been identified, individual limits should be set for each identified impurity. A limit for total unidentified impurities should also be specified. These limits should be established based on actual data for qualification batches. A justification for proposed limits should be given. A revised limit of for the total of all impurities should be implemented. Please provide revised tests and specifications sheets and revised stability protocols to reflect the above.

Orig. NDA 20-632
cc: HFD-510/Division file/M.Haber/S.Moore/J.Gibbs/Y.Chiu /M.Hess
HFD-570/G.Poochikian

NOV - 4 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-632 **DATE REVIEWED:** 4-November-96

CHEMISTRY REVIEW #: 3 **REVIEWER:** Martin Haber, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	7-AUG-95	9-AUG-95	16-AUG-95
AMENDMENT	25-OCT-96	28-OCT-96	
AMENDMENT	29-OCT-96	31-OCT-96	

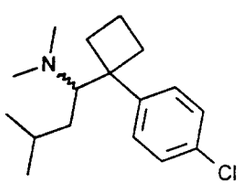
NAME & ADDRESS OF SPONSOR: Knoll Pharmaceutical Company
3000 Continental Drive, North
Mount Olive, NJ 07828-1234 (201) 331-7561

DRUG PRODUCT NAME:

Proprietary:	Meridia
Nonproprietary:	Sibutramine hydrochloride monohydrate
Code Name/#:	BTS 54 524
Chem.Type/Therapeutic.Class:	Type 1, NME/ Class S

PHARMACOL. CATEGORY/INDICATION: Treatment of obesity
DOSAGE FORM: Capsules
STRENGTHS: 5, 10, 15 and 20 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: __X__ **Rx** ___ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-Cyclobutanemethanamine,1-(4-chlorophenyl)-*N,N*-dimethyl -α-(2-methylpropyl)-,hydrochloride, monohydrate; *N*-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}-*N,N*-dimethylamine hydrochloride monohydrate
CAS #: 125494-59-9, $C_{17}H_{29}Cl_2NO$, mol. wt. 334.33



REMARKS:
The 10/25/96 amendment provides for revised draft package labels for the 5, 10, 15 and 20 mg strengths. The 10/29/96 amendment provides for incorporation of into the NDA.

CONCLUSIONS & RECOMMENDATIONS:
From a chemistry viewpoint the information provided is satisfactory. No action indicated. A copy of the Chemistry Review of should be included into the NDA file since this material has now been submitted to the NDA. The part of the draft action letter requesting draft carton labeling should be deleted.

Orig. NDA # 20-632
cc: HFD-510/Division file/S.Moore/M.Haber/M.Hess
ONDC/ODEII/Y.Chiu

Martin Haber, Ph.D.
Review Chemist

R/D Init by: Dr. Moore, Team Leader Chemist

11/4/96

OCT 28 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-632 **DATE REVIEWED:** 28-October-96

CHEMISTRY REVIEW #: 2 **REVIEWER:** Martin Haber, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	7-AUG-95	9-AUG-95	16-AUG-95
AMENDMENT	15-OCT-96	18-OCT-96	

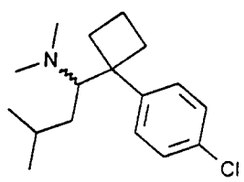
NAME & ADDRESS OF SPONSOR: Knoll Pharmaceutical Company
3000 Continental Drive, North
Mount Olive, NJ 07828-1234 (201) 331-7561

DRUG PRODUCT NAME:

Proprietary:	Meridia
Nonproprietary:	Sibutramine hydrochloride monohydrate
Code Name/#:	BTS 54 524
Chem.Type/Therapeutic.Class:	Type 1, NME/ Class S

PHARMACOL. CATEGORY/INDICATION: Treatment of obesity
DOSAGE FORM: Capsules
STRENGTHS: 5, 10, 15 and 20 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: X Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-Cyclobutanemethanamine,1-(4-chlorophenyl)-*N,N*-dimethyl -α-(2-methylpropyl)-,hydrochloride, monohydrate; *N*-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}-*N,N*-dimethylamine hydrochloride monohydrate
CAS #: 125494-59-9, $C_{17}H_{29}Cl_2NO$, mol. wt. 334.33



REMARKS:
The 10/15/96 amendment provides for additional stability data for the 5, 10 and 15 mg strengths (18 months at 25°C and 12 months at 30°C).

CONCLUSIONS & RECOMMENDATIONS:
From a chemistry viewpoint the information provided is satisfactory. No action indicated.

Orig. NDA # 20-632
cc: HFD-510/Division file/S.Moore/M.Haber/M.Hess
ONDC/ODEII/Y.Chiu

Martin Haber, Ph.D.
Review Chemist

R/D Init by: Dr. Moore, Team Leader Chemist

10/28/96

OCT 10 1996

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-632 **DATE REVIEWED:** 9-October-96

CHEMISTRY REVIEW #: 1 **REVIEWER:** Martin Haber, Ph.D.

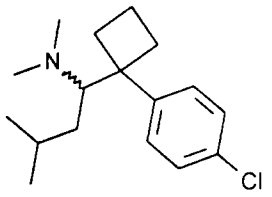
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	7-AUG-95	9-AUG-95	16-AUG-95
AMENDMENT	13-DEC-95	18-DEC-95	
AMENDMENT	10-MAY-96	13-MAY-96	

NAME & ADDRESS OF SPONSOR: Knoll Pharmaceutical Company
8800 Ellerbe Road
Shreveport, LA 71106 (318) 861-8375

DRUG PRODUCT NAME:

Proprietary:	Meridia Capsules
Nonproprietary:	Sibutramine hydrochloride monohydrate
Code Name/#:	BTS 54 524
Chem.Type/Therapeutic.Class:	Type 1, NME/ Class S

PHARMACOL. CATEGORY/INDICATION: Treatment of obesity
DOSAGE FORM: Capsules
STRENGTHS: 5, 10, 15, and 20 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: X Rx ___ OTC



CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(±)-Cyclobutanemethanamine,1-(4-chlorophenyl)-*N,N*-dimethyl -α-(2-methylpropyl)-,hydrochloride, monohydrate; *N*-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}-*N,N*-dimethylamine hydrochloride monohydrate
CAS #: 125494-59-9, $C_{17}H_{29}Cl_2NO$, mol. wt. 334.33

REMARKS:
See next page.

CONCLUSIONS & RECOMMENDATIONS:
From a chemistry viewpoint the application is approvable. EA Consult is pending. All inspections are acceptable as of 4/20/96. Methods Validation is pending. Biopharmaceutical information is satisfactory, see review dated 5/7/96. Comments from Biopharm. should be communicated to the firm.

Orig. NDA # 20-632
cc: HFD-510/Division file/S.Moore/M.Haber/M.Hess
ONDC/ODEII/Y.Chiu
R/D Init by: Dr. Moore, Team Leader Chemist

Martin Haber, Ph.D.
Review Chemist

filename: 20632_1.nda

10/10/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Meridia™
(Sibutramine Hydrochloride Monohydrate)
Capsule
NDA 20-632

Knoll Pharmaceutical Company

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Metabolic and Endocrine Drug Products
(HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-632

Meridia™

(Sibutramine Hydrochloride Monohydrate)

Capsule

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research,has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Meridia, Knoll Pharmaceutical Company has conducted a number of environmental studies and prepared an environmental assessment (attached) in accordance with 21 CFR 25.31a(a), which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Sibutramine Hydrochloride Monohydrate is a which is administered as a capsule in the long term treatment of obesity and should be used in conjunction with diet and exercise as part of a weight management program. The drug substance will be manufactured by . The drug product manufacture will take place at Knoll Pharmaceutical Company, Shreveport, Louisiana. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Sibutramine Hydrochloride Monohydrate may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The firm conducted fate studies which indicate that the substance is susceptible to photodegradation. Environmental effects studies indicate that the expected environmental concentration is many orders of magnitude less than the concentration that caused effects in standard test organisms.

Disposal of the drug may result from out of specification lots, discarding of unused or expired

product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be returned to Knoll Pharmaceutical Company and disposed as medical waste by incineration in compliance with all applicable regulatory requirements. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

10/4/96
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

10/4/96
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)

ENVIRONMENTAL ASSESSMENT

ITEM 1: DATE

August 27, 1996

ITEM 2: NAME OF APPLICANT

Knoll Pharmaceutical Company
(Formerly Boots Pharmaceuticals, Inc.)

ITEM 3: ADDRESS

P.O. Box 6750
Shreveport, LA 71136-6750

ITEM 4: DESCRIPTION OF PROPOSED ACTION

a. Request

Knoll Pharmaceutical is filing NDA 20-632, requesting approval to market MERIDIA ™ (sibutramine hydrochloride monohydrate) Capsules. MERIDIA capsules are indicated for the long-term treatment of obesity and should be used in conjunction with diet and exercise as part of a weight management program. Each MERIDIA capsule contains 5 mg, 10 mg, 15 mg or 20 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients, lactose monohydrate, NF ; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard gelatin capsule. The filing of the NDA was needed to obtain approval for the marketing of the drug product in the United States.

The capsules containing one active ingredient will be manfactured and packaged by Knoll Pharmaceutical Company at 8800 Ellerbe Road, Shreveport, Louisiana. The MERIDIA capsules will be packaged in

for commerical distribution. All capsules strengths will be available in a with a All capsule strengths will be available in blister as sample packs which will have the same composition and cavity size. The blister is composed of a

on the exterior of the cavity. The backing material is composed of

b. Proposed use

We plan to market the product in the United States where it will be limited to a physican's prescription and supplied to individual patients by pharmacies, both independent and hospital-affliliated.

c. Locations where the product will be manufactured and packaged

1. Manufacturing of the drug substance sibutramine hydrochloride will take place at the following facilities:

The facility in the is located on the edge of a major conurbation on flat terrain in a temperate climate. Please refer for further information on the site on which this facility is located.

The facility in the is located in a rural area on reasonably flat terrain and in a temperate climate. Please refer to for further information on this facility.

The facilities each conduct part of the synthesis of the drug substance.

2. Formulation and packaging of the sibutramine capsule product will take place at the following facility:

Knoll Pharmaceutical Company
8800 Ellerbe Road
Shreveport, LA 71106

This facility is located in a temperate zone, on relatively flat terrain. The surrounding land can be characterized by the following uses: commercial development, light industry, and limited residential tracts.

d. Locations where the drug product will be disposed

Disposal of rejected sibutramine hydrochloride monohydrate in the or of unused/ rejected sibutramine capsules in the United States will be as solid waste in either landfills or incinerators.

Sibutramine capsules are expected to be used throughout the United States in a pattern corresponding to national trends in population density. The fifth year estimate of market volume for the United States is listed in the confidential Appendix C. The drug and its metabolites, excreted in human waste, are expected to be disposed of in household wastewater.

ITEM 5: IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Sibutramine hydrochloride monohydrate is the active ingredient in sibutramine capsules.

a. Name:

Sibutramine hydrochloride monohydrate

b. International non-proprietary name:

The international non-proprietary name for the free base is "sibutramine".

c. Chemical name:

N-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine hydrochloride monohydrate

d. CAS registry numbers:

125494-59-9 (sibutramine hydrochloride monohydrate)
84485-00-7 (sibutramine hydrochloride anhydrous)
106650-56-0 (sibutramine)

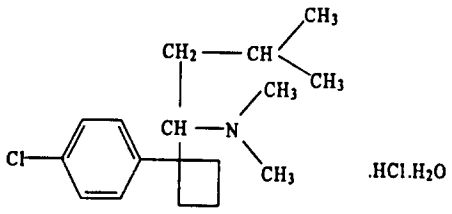
e. Molecular formula:

$C_{17}H_{29}Cl_2NO$

f. Molecular weight

334.33

g. Structural formula



h. Physical description

A white to cream crystalline powder

i. Impurities

j. **Material Safety Data Sheet:**

A non-confidential material safety data sheet for sibutramine hydrochloride monohydrate is provided in Appendix D.

ITEM 6: INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

a. **Substances introduced to the environment during drug substance manufacture.**

Substances used in the manufacture of sibutramine hydrochloride monohydrate are listed in confidential Appendix D. Information in the form of Material Safety Data Sheets, on each substance are also provided.

The quantities of materials used in the manufacture of the drug substance, and the quantity of material emitted are provided in confidential Appendix D. These figures are based upon one campaign, and may vary slightly from campaign to campaign.

The quantities of materials introduced into the environment is reduced by recycling in the process. It is a specific policy to recycle materials, wherever possible, to minimize emissions into the environment.

The information in confidential Appendix D details the materials recycled. It also identifies several waste streams where use of recycling is being considered.

A discussion of the applicable environmental regulations may be found in Appendix D. The manufacturing facility is currently in compliance with regulatory requirements and FDA approval of the use of sibutramine hydrochloride in the U.S. is not expected to adversely affect compliance. The certification of compliance for foreign facilities is provided as a non-confidential document in Appendix D.

b. **Substances introduced to the environment during formulation and packaging of sibutramine capsules at the Shreveport facility.**

Substances released to the environment associated with the formulation and packaging of sibutramine capsules at the Shreveport facility are described in Appendix E.

A discussion of the applicable environmental and occupational regulations may also be found in Appendix E. The formulation facility is currently in compliance with the corresponding regulatory requirements and FDA approval of the use of sibutramine hydrochloride in the U.S. is not expected to adversely affect compliance.

c. Introductions of sibutramine hydrochloride to the environment through its use as a weight loss agent.

ITEM 7: FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

a. Summary

The environmental fate of sibutramine hydrochloride and its by-products will depend upon the waste stream entering the environment, as described in Items 4 and 6, manufacturing emissions will be transferred to landfills, incinerated, or transferred to wastewater treatment facilities in compliance with all federal, state and local regulatory requirements. Unused product (e.g., product beyond expiration, shipping-damaged product, etc.) will be returned to Knoll

Pharmaceutical Company and disposed as medical waste by incineration in compliance with all applicable regulatory requirements.

Consumed product (excreted in the urine and feces) will enter the environment via either municipal wastewater or on-site (e.g., septic systems) treatment. There may also be some unused product (believed to be of insignificant volume) flushed into wastewater by patients.

Sibutramine hydrochloride is soluble in water and has a

The compound has an octanol/water partition coefficient of These values indicate a slight potential for sibutramine HCl to bioaccumulate or sorb to soils. The low vapor pressure suggests little potential for volatilization in the solid state; however, the compound demonstrates a tendency to The compound is not subject to Appendix A, Table 1, lists the measured physical/chemical properties that are the basis for these conclusions.

Studies with sibutramine hydrochloride demonstrated its Sibutramine photolyzed with the formation of at least degradation products. It can be concluded that photodegradation may be an important removal mechanism of sibutramine in aqueous media, especially at environmentally
Aerobic aquatic biodegradation studies demonstrated that sibutramine hydrochloride slowly mineralized by day We have conducted a Henry's Law Constant study to quantify the observations of volatility as seen in the aerobic biodegradation study. The Henry's Law Constant for

It is expected that any sibutramine hydrochloride or metabolites, introduced to wastewater streams, is likely to be photodegraded on initial exposure in a waste treatment facility. Any undepleted compound will be further diluted upon introduction to a Publicly Operated Treatment Works (POTW) and the already low concentration of material is expected to be photolyzed in the holding tanks of the

POTW. Any water soluble compound remaining would be expected to partition to the activated sludge component at the water/sludge interface where it would undergo further aerobic biodegradation and not be discharged to surface waters.

b. Physical/chemical property data applicable to an assessment of the fate of sibutramine hydrochloride

The general methodologies and results of each of the physical/chemical properties and environmental fate studies are described below. Full reports are included in appendices as noted.

1. Water solubility

Confidential Appendix G is a report of a water solubility study performed with sibutramine hydrochloride.

Triplicate sample analysis were conducted in buffers, and four replicate sample analyses were conducted in pH . The solutions were considered at equilibrium when there was less than a in concentration between consecutive samplings. The solutions were then centrifuged and analyzed for sibutramine. The results of this study indicate the water solubility of sibutramine in

2. Melting temperature

Confidential Appendix H contains the study report for the melting temperature of sibutramine hydrochloride monohydrate. Melting point was determined using a hot stage microscope as recommended in the FDA Technical Assistance Document 3.06. The average melting temperature was determined to be 187.46°C with a range of and a standard deviation of 0.033.

3. Density

Confidential Appendix I contains the study report for the density of sibutramine hydrochloride monohydrate. Density was determined using a as recommended in the FDA Technical Assistance Document 3.07. The mean density value for the test compound is

4. Dissociation Constant

Confidential Appendix J contains the study report for the determination of the dissociation constant of sibutramine hydrochloride monohydrate. The pKa value was determined to be using the described in the FDA Technical Assistance Document 3.04.

5.

Confidential Appendix K contains the study report for the determination of the of sibutramine hydrochloride monohydrate. The tests were conducted at as recommended in the FDA Technical Assistance Document The test compound showed However, no absorption maxima was detected between

6. Octanol/Water Partition Coefficient

Confidential Appendix L contains the study report for the determination of the octanol/water partition coefficient of sibutramine hydrochloride monohydrate at pH 5, 7, and 9. The tests were conducted as recommended by the FDA Technical Assistance Document 3.02. The test compound

7. Vapor Pressure

Confidential Appendix M contains the study report for the vapor pressure estimate of sibutramine hydrochloride monohydrate. The vapor pressure of sibutramine hydrochloride monohydrate was determined by comparing the times of duration of the mass spectrum of the test compound to the times of duration of the

mass spectrum of ibuprofen (described by Ertel, *et al*, 1990). The vapor pressure of sibutramine hydrochloride is estimated to be

8. Henry's Law Constant

Confidential Appendix N contains the study report for the Henry's Law Constant of monohydrate. The study was conducted according to U.S. EPA TSCA Guideline The Henry's Law Constant for

9. Hydrolysis

Confidential Appendix O contains the study report for the hydrolysis of in aqueous media. The study was conducted according to the FDA Technical Assistance Document 3.09. The results of this study demonstrate the sibutramine HCl

10. Soil/Sediment Adsorption/Desorption

Confidential Appendix P contains the study report for the determination of the soil/sediment adsorption/desorption of The test was conducted according to FDA Technical Assistance Document 3.08 on three soil types (loam, sandy loam, and silt loam) at

soils, respectively, indicate that sibutramine would be classified being when compared with other chemicals on soil.

11. Aerobic Aquatic Biodegradation

Confidential Appendix Q contains the study report for determination of the aerobic aquatic biodegradation of ^{14}C-sibutramine hydrochloride monohydrate. The study was conducted according to FDA Technical Assistance Document 3.11. The test chemical, was completely volatilized and the majority of the volatile material was still the parent compound. By day 7, the test chemical was slowly mineralized where the reference

chemical

12. Photodegradation

Confidential Appendix R contains the study report for the determination of aqueous photodegradation of

The study was conducted according to the FDA Technical Assistance Document 3.10. The results of this study demonstrate that sibutramine undergoes photodegradation in aqueous media over a range of pH values, with experimentally measured half-lives of hours for pH respectively. Sibutramine photolyzed with the formation of at least eight quantifiable degradation products during the study. Thus, it can be concluded that photodegradation may be an important removal mechanism of sibutramine in the especially at environmentally relevant pH levels of

13. Aerobic Soil Biodegradation

Confidential Appendix U contains the study report for the aerobic soil biodegradation of

The study was conducted according to the FDA Technical Assistance Document 3.12. The results of this study demonstrate that sibutramine HCl is subject to

c. Prediction of Environmental Concentrations of Sibutramine Hydrochloride Monohydrate and Its Metabolites as a Result of Its Use and Disposal.

Sibutramine hydrochloride monohydrate and its metabolites excreted in human waste to waste water are expected to be photodegraded while in the pretreatment wastewater. Any small amount not degraded prior to wastewater treatment is expected to degrade during the treatment process. The small amount of material exposed to activated sludge is expected to adhere to the sludge and not be discharged to surface waters. Sibutramine hydrochloride and its metabolites should approach a zero concentration level after exposure to sunlight and the action of the activated sludge on any remaining material.

ITEM 8: ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

a. Summary

The environmental effects of sibutramine hydrochloride monohydrate were investigated in two studies: Microbial Growth Inhibition (FDA, TAD 4.02) and *Daphnia magna* Acute Toxicity (FDA TAD 4.08). Toxicity data indicate at the estimated environmental concentration expected to enter municipal wastewater effluent, sibutramine hydrochloride is unlikely to pose any significant threat to the environment. The EEC is determined in the *Daphnia magna* Acute Toxicity study and is not likely to inhibit microbial growth at the expected concentrations.

b. Environmental Effects Data Applicable to an Assessment of the Toxicity of Sibutramine Hydrochloride Monohydrate.

The general methodologies and results of each of the environmental effects studies are described below. Full reports are included in appendices as noted.

1. Microbial Growth Inhibition (FDA TAD 4.02)

Confidential Appendix S is a report of a Microbial Growth Inhibition Study conducted with sibutramine hydrochloride monohydrate. Sibutramine was tested at nominal concentrations of 120, 60, 30, 15, and 0 mg/L. The test chemical sibutramine hydrochloride monohydrate showed no inhibition for *Pseudomonas, Bacillus, Azotobacter Aspergillus, Penicillium* and *Chaetomium* at the maximum concentration of

Hence
Inhibitory Concentration (MIC)

However, the blue-green alga *Anabaena flos-aquae* showed inhibition at

2. *Daphnia magna* Acute Toxicity (FDA TAD 4.08)

Confidential Appendix T is a report of a 48-hour Flow-Through *Daphnia magna* Acute Toxicity Study conducted with sibutramine hydrochloride monohydrate. The nominal test concentrations for this study were 0.24, 0.48, 1.0, 2.0, and 4.0 mg/L. The mean measured concentration levels were

respectively of the nominal test concentrations. The 48-hour median effective concentration (EC_{50}) for *Daphnia magna* exposed to sibutramine hydrochloride was shown to be
A 48-hour EC_{50} is the concentration of the ttest chemical in water

. A 48-hour no-observed effect level was determined

Item 9: USE OF RESOURCES AND ENERGY

There are no significant land or mineral uses associated with the proposed action. The manufacture, packaging, and distribution of sibutramine hydrochloride monohydrate and sibutramine capsules will take place using existing facilities. There are no threatened or endangered species issues or properties listed in or eligible for listing in the National Register of Historic Places in relation to the proposed action. The energy and utility usage in the manufacture of sibutramine hydrochloride monohydrate is detailed in confidential Appendix C.

ITEM 10: MITIGATION MEASURES

Appendices D and E list the environmental controls that will be in place for the manufacture of sibutramine hydrochloride monohydrate and sibutramine capsules. Knoll plans to recycle, as much as possible, the wastes generated during these processes. Most of the solvents used during the processes are captured and recycled. Wastes generated as a result of material not meeting specification will be disposed of in appropriate landfill facilities to eliminate the potential for environmental exposure.

Wastes generated as a result of returned marketed product (i.e., material past expiration date) will be handled as medical waste and incinerated in an approved facility as described in Appendix E. No significant environmental impacts are anticipated as a result of patient use.

ITEM 11: ALTERNATIVES TO THE PROPOSED ACTION

The use of sibutramine as a weight loss agent in obese patients is considered an alternative therapy whose benefits outweigh the inherent risks of other pharmacologic treatment for this debilitating condition. A decision by the agency to not approve commercial distribution of this drug would result in

depravation of a potentially beneficial treatment to this specific patient population. Because no potential environmental impacts are expected, there are no reasonable alternatives to the proposed action.

ITEM 12: LIST OF PREPARERS

(Curriculum vitae provided in Appendix V)

Michael Gill, B.S., Regulatory Associate, Knoll Pharmaceutical Company. Seven years analytical chemistry experience, seven years regulatory affairs experience for the pharmaceutical industry.

ITEM 13: CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the firm or agency responsible for the preparation of the environmental assessment.

Abraham Varghese, Ph.D.
Associate Director, Regulatory Affairs

8-27-96
Date

APPEARS THIS WAY
ON ORIGINAL

ITEM 14: REFERENCES

Food and Drug Administration (FDA) March 1987. *Environmental Assessment Technical Assistance Handbook.*

Lyman, W.J., W.F. Reehl, and D.H. Rosenblatt (eds.). *Handbook of Chemical Property Estimation Methods. American Chemical Society, Washington, DC.*

ITEM 15: APPENDICES

Confidential Appendices A-V are attached.

List of CONFIDENTIAL Appendices

Appendix	Subject	Vol.	Page
A	Data Summary Tables (Non-confidential) see FDA addendum 10/4/94	1.6	0001
B	Confidential Pharmacokinetics Data Used for Modeling Metabolites in Wastewater.	1.6	0008
C	Confidential Information on Market Volume, Modeled Concentrations of Metabolites in Wastewater, Impurities, and Energy Requirements for Manufacture.	1.6	0031
D	Confidential Information on Environmental Introductions and Applicable Environmental and Occupational Regulations for the Knoll Pharma Chemicals Manufacturing Facility in the U.K. pages 35, 36, 60, 61 non-confidential see FDA addendum 10/4/94	1.6	0035
E	Confidential Information on Environmental Introductions and Applicable Environmental and Occupational Regulations for the Shreveport Final Product Formulation Facility. pages 183, 184A, 184B non-confidential see FDA addendum 10/4/94	1.6-	0183
F	Validation of Analytical Test Methods	1.7 - 1.8	0001
G	Water Solubility Study Report (FDA 3.01)	1.9 - 1.13	0001
H	Melting Temperature Study Report (FDA 3.06)	1.14	0001
I	Density Study Report (FDA 3.07)	1.14	0005
J	Dissociation Constant Study Report (FDA 3.04)	1.14	0010
K	UV/VIS Absorption Spectrum (FDA 3.05)	1.14	0294
L	Octanol/Water Partition Coefficient Study Report (FDA 3.02)	1.15	0001
M	Vapor Pressure Study Report (FDA 3.03)	1.16	0001
N	Henry's Law Constant Report	1.16	0006
O	Hydrolysis Study Report (FDA 3.09)	1.17	0001

List of CONFIDENTIAL Appendices (continued)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

ADDENDUM

DATE: October 4, 1996

FROM: Carl J. Berninger, Ph.D. through Ms. Nancy Sager
HFD-357

SUBJECT: Addendum to Environmental Assessment for Merida™

TO: File

The Environmental Assessment submitted with a cover letter dated 8/27/96 includes a clearly designated non-confidential public Assessment. That public Assessment uses the inappropriate word "confidential" on pages 15, 16, 17, 0035, and 0183. The cover letter confirms the firm's intention to make information in Appendix A, D and E public.

Appendix A

Data Summary Tables

DATA SUMMARY TABLES

PRODUCT CHEMISTRY

TABLE 1 Chemical/Physical Properties of Sibutramine Hydrochloride Monohydrate		
Property	**Result**	**Appendix Containing Study Report**
Water solubility (FDA 3.01)	0.541 mg/mL @ pH 5 0.112 mg/mL @ pH 7 7.5×10^{-4} mg/mL @ pH 9	G
Dissociation constant (pKa) (FDA 3.04)	9.5	J
Octanol/water partition coefficient (K_{ow}) (FDA 3.02)	pH 5 47.6 pH 7 655 pH 9 816	L
Vapor pressure (FDA 3.03)	3×10^{-8} torr	M
Henry's Law Constant	0.0240 L · atm/mole	N
Hydrolysis (FDA 3.09)	Not subject to hydrolysis	O
UV/VIS Absorption Spectrum (FDA 3.05)	Absorption maxima at 272 nm and 226 nm No absorption maximum between 290 and 800 nm	K
Melting Point (FDA 3.06)	187.46°C	H
Density (FDA 3.07)	1.19 g/cc	I

FATE CHEMISTRY AND BIODEGRADATION RESULTS

TABLE 2
Photodegradation (FDA 3.10)
Estimated Half-Lives in Flat Bodies of Water for Sibutramine as a Function of Latitude and Season Based on Measured Intensity Quantum Yield Values

pH-Latitude	Spring Half-Life (hours)	Summer Half-Life (hours)	Fall Half-Life (hours)	Winter Half-Life (hours)
pH 5-20° N	36.6	34.5	44.9	53.9
pH 5-30° N	37.7	33.9	52.8	70.4
pH 5-40° N	40.3	34.1	67.2	106.3
pH 5-50° N	45.5	35.2	97.4	200.6
pH 7-20° N	2.71	2.57	3.26	2.42
pH 7-30° N	2.88	2.62	3.91	5.14
pH 7-40° N	2.93	2.52	4.70	7.27
pH 7-50° N	3.24	2.57	5.69	14.0
pH 9-20° N	0.824	0.779	0.998	0.744
pH 9-30° N	0.814	0.736	1.12	1.47
pH 9-40° N	0.895	0.765	1.46	2.27
pH 9-50° N	1.01	0.783	1.94	4.38

TABLE 3

Aerobic Aquatic Biodegradation (FDA 3.11)

Result
The test chemical, ^{14}C-sibutramine HCl, was completely volatilized and the majority of the volatile material was still the parent compound. By day 7, the test chemical was slowly mineralized (5.29% $^{14}CO_2$ production).

FATE CHEMISTRY AND BIODEGRADATION RESULTS

TABLE 4

Soil/Sediment Adsorption-Desorption of Sibutramine Hydrochloride (FDA 3.08)

Results

Soil Type	% Organic Matter	% Organic Carbon	Adsorption		Desorption		n
			K_d[1]	K_{oc}[2]	K_d[1]	K_{oc}[2]	Ads/Des
Loam	6.5	3.78	462	12237	523	13851	0.973/ 0.976
Sandy Loam	3.1	1.80	705	39093	760	42154	0.819/ 0.826
Silt Loam	3.0	1.74	303	17383	305	17481	0.820/ 0.830

1. $K_d = \frac{\text{chemical sorbed}}{\text{chemical in solution at equiliburium}}$

   expressed as $\frac{\mu g/g \text{ soil}}{\mu g/g \text{ solution}}$

2. $K_{oc} = \frac{K_d}{\%\text{ organic carbon}} \times 100$

   or

   $K_{oc} = \frac{\mu g \text{ chemical sorbed/g soil organic carbon}}{\mu g \text{ chemical dissolved at equilibrium/g solution}}$

DATA SUMMARY TABLES

FATE CHEMISTRY AND BIODEGRADATION RESULTS

TABLE 5

Aerobic Biodegradation of ^{14}C-Sibutramine HCl in Soils (FDA 3.12)

Soil Type	Percent $^{14}CO_2$ Evolution at Termination (Day 70) Mean/S.D.	Mass Balance Mean/S.D.
Loam	44.1/ 2.1	96.0/ 1.9
Sandy Loam	21.4/ 4.4	93.9/ 3.4
Silt Loam	48.0/ 3.6	101/ 1.5

DATA SUMMARY TABLES

TOXICOLOGY/EFFECTS RESULTS

TABLE 6

Growth on Test Plates Used to Determine the MIC Value of Sibutramine HCl

Organism	Replicate	Solvent Blank	Control	Concentration of Sibutramine HCl (mg/L) 15	30	60	120	MIC
Pseudomonas fluorescens	A	+	+	+	+	+	+	NIO
	B	+	+	+	+	+	+	NIO
	C	+	+	+	+	+	+	NIO
Bacillus megaterium	A	+	+	+	+	+	+	NIO
	B	+	+	+	+	+	+	NIO
	C	+	+	+	+	+	+	NIO
Azotobacter chroococcum	A	+	+	+	+	+	+	NIO
	B	+	+	+	+	+	+	NIO
	C	+	+	+	+	+	+	NIO
Anabaena flos-aquae	A	+	+	+	+	-	-	60
	B	+	+	+	+	-	-	60
	C	+	+	+	+	-	-	60
Aspergillus clavatus	A	+	+	+	+	+	+	NIO
	B	+	+	+	+	+	+	NIO
	C	+	+	+	+	+	+	NIO
Penicillium canescens	A	+	+	+	+	+	+	NIO
	B	+	+	+	+	+	+	NIO
	C	+	+	+	+	+	+	NIO
Chaetomium globosam	A	+	+	+	+	+	+	NIO
	B	+	+	+	+	+	+	NIO
	C	+	+	+	+	+	+	NIO

+= Positive GrowthAll plates were observed on May 16, 1994
-= No Growth
MIC= Minimum Inhibitory Concentration
NIO= No Inhibition Observed

DATA SUMMARY TABLES

TOXICOLOGY/EFFECTS RESULTS

TABLE 7

Daphnia magna Acute Toxicity (FDA 4.08)

The 48-Hour Flow-Through Toxicity of Sibutramine Hydrochloride to *Daphnia magna*

	EC_{50} (mg/L) (95% confidence limits)	
Test Compound	24-Hour	48-Hour
Sibutramine Hydrochloride	> 3.1[a] (b)	1.8[c] (1.6 and 2.1 mg/L)

[a] Estimated value

[b] 95% confidence limits could not be determined

[c] EC_{50} and 95% confidence limits were determined using the moving average method.

Note: The 48-hour no-observed effect concentration was estimated to be 0.19 mg/L

Appendix D

Non-Confidential Information on Environmental Introductions and Applicable Environmental and Occupational Regulations for the Knoll Pharma Chemicals Manufacturing Facility in the U.K.

See FOA addendum 10/4/94

Knoll Pharmaceuticals a branch of BASFIN Corporation

Knoll Pharmaceuticals, 1 Thane Road West,
Nottingham, NG2 3AA England
Tel : (0115) 950 6111

DRP/gr
8th July 1996

BASF Pharma

Environmental Mngt & Safety
D83
Beeston

Direct Line:
0115 9594121
Fax No:
0115 9594980

TO WHOM IT MAY CONCERN

Manufacture of Sibutramine Hydrochloride Monohydrate

The early stages of the manufacture of sibutramine hydrochloride monohydrate are carried out on the Knoll Pharma Chemicals site in Beeston, Nottinghamshire, and the latter stages at their site at Cramlington in Northumberland.

Aqueous effluent releases are controlled by Severn-Trent Water Limited, Northumbrian Water Limited and the Environment Agency. These bodies operate primarily under the Water Industry Act 1991 and the Water Resources Act 1991. Relevant and hazardous substances are listed and each is controlled by means of "consent" levels which are monitored in-house and by the appropriate regulatory body.

Aerial emissions and waste for disposal are controlled by Environmental Agency and the processes are authorised by them under the Environmental Protection Act 1990.

I certify that the sites comply with all relevant legislation and Company policy demands that a full response to regulatory requirements is made.

D R Parsons
Safety and Environmental Manager

0036

SAFETY DATA SHEET

Knoll Pharma Chemicals
A business within Knoll Pharmaceuticals, a branch of BASFIN Corporation

knoll

BASF Pharma

SIBUTRAMINE HYDROCHLORIDE

1. IDENTIFICATION OF SUBSTANCE/ PREPARATION

Product Name	:	SIBUTRAMINE HYDROCHLORIDE
Molecular Formula	:	$C_{17}H_{29}NOCl_2$
Alternative Names	:	N-{1-[1-(4-Chlorophenyl)cyclobutyl]-3-methylbutyl} N,N-dimethylamine hydrochloride, monohydrate.
CAS No.	:	125494-59-9
EINECS No.	:	Not found.
Uses	:	Anti - obesity agent.
Company Identification	:	Knoll Pharmaceuticals, a branch of BASFIN Corporation. 1 Thane Road West, Nottingham NG2 3AA, England.
Emergency Telephone	:	*(0115) 912 2222*

2. COMPOSITION/ INFORMATION ON INGREDIENTS

Component	Hazard Class	Risk Phrases	%
Sibutramine hydrochloride monohydrate	Toxic (T)	R23/24/25, R36/37.	>98

3. HAZARDS

Health	Has CNS stimulant activity and should be regarded as toxic. Irritating to eyes. Due to its fine particulate nature, may cause irritation to the respiratory tract if inhaled. A high standard of industrial hygiene must be maintained.
Fire and Explosion	Stable at normal temperature. Combustible. St 2 dust explosion class (i.e strongly explosible).
Environment	No relevant data available.

4. FIRST-AID

Eyes	Immediately irrigate with water for at least 10 minutes and obtain medical attention.
Skin	Immediately drench with water. Remove contaminated clothing, and continue to irrigate with water. If irritation develops, obtain medical attention.
If Swallowed	Wash out mouth thoroughly with water, give sips of water to drink. Obtain medical attention.
If Inhaled	Remove to fresh air. If discomfort persists obtain medical attention.

5. FIRE FIGHTING

The product will burn in air, producing toxic gases. Self-contained breathing apparatus should be provided for firemen fighting fires in confined spaces.
Water spray, foam, carbon dioxide and dry chemical powder are suitable extinguishing agents.

6. ACCIDENTAL RELEASE

Personal Precautions	Wear suitable approved respiratory protection, PVC or rubber gloves and goggles.
Environmental Precautions	Prevent entry into drains, watercourses etc.
Methods For Cleaning Up	Immediately collect up or vacuum clean (avoid creating a dust cloud) and remove the spillage to a polythene lined container. Seal and send for disposal. Clean the area with detergent and water.

7. HANDLING AND STORAGE

Handling	Avoid contact with skin, eyes and clothing. Avoid ingestion and inhalation. Where there is a risk of personal contact, protective clothing including suitable approved respiratory protection, PVC or rubber gloves, and chemical safety goggles, must be worn. Take precautions against static discharge. Provide dust explosion protection where necessary.
Storage	Store at ambient temperatures in sealed containers away from: (i) oxidising agents; (ii) heat and sources of ignition; (iii) food, drink and animal feedstuffs.

0060

(over)

8. EXPOSURE CONTROLS/ PERSONAL PROTECTION

Occupational Exposure Limits	An in-house exposure level of 0.05 mg/m³ has been established (4/11/94).
Respiratory Protection	Minimum is approved particulate respirator, but air-fed hood preferred.
Hand Protection	PVC or rubber gloves.
Eye Protection	Chemical safety goggles.
Skin Protection	Overall or disposable coverall.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	A white crystalline powder.
Odour	Characteristic 'damp' odour.
Molecular Weight	316.31
Melting Point (°C)	191 to 192°C
Relative Density	0.33 g/ml
Solubility In Water	Slightly soluble.
Solubility In Other Solvents	Ethanol : very soluble.

10. STABILITY AND REACTIVITY

Stability/ Reactivity	Crystalline changes occur at temperatures up to 150°C, but thermally stable at least to its melting point.
Conditions To Avoid	Heat and sources of ignition.
Materials To Avoid	Oxidising agents.
Hazardous Decomposition Products	Hydrogen chloride and oxides of nitrogen.

11. TOXICOLOGICAL INFORMATION

Acute oral toxicity studies in rats, dogs and monkeys revealed no effect at 10 mg/kg, though higher doses caused CNS stimulant effects. The lowest lethal dose in rats was 100 mg/kg. In repeated-dose studies, food consumption and bodyweight gain were reduced.
There were no adverse effects on fertility or embryonic development in rats, though high doses decreased perinatal survival.
There was no evidence of mutagenicity, and no carcinogenic effects in rats or mice though there was an increased incidence of benign interstitial cell tumours in male rats.
Sibutramine was irritant to rabbit eyes but not to intact skin. It was classified as a weak (Grade 1) sensitizer in a guinea pig maximisation test. In acute dermal and inhalation studies in rats, there was evidence of systemic exposure.

12. ECOLOGICAL INFORMATION

No relevant data available.

13. DISPOSAL CONSIDERATIONS

Dispose of in accordance with current legislation, preferably using high temperature incineration. Contaminated empty packaging materials should be treated in a similar manner.

14. TRANSPORT INFORMATION

PSN / UN Number : Toxic solid, organic, n.o.s. / 2811 UN Hazard Class : 6.1 UN Packing Group : III

15. REGULATORY INFORMATION

Classification of risk	Toxic (T)	
Risk phrases	R23/24/25	Toxic by inhalation, in contact with skin and if swallowed.
	R36/37	Irritating to eyes and respiratory system.
Safety phrases	S36/37/39	Wear suitable protective clothing, gloves and eye/face protection.
	S45	In case of accident or if you feel unwell, seek medical advice immediately (show label where possible).

16. OTHER INFORMATION

* Indicates additional or recently revised data.

Appendix E

Confidential Information on Environmental Introductions and Applicable Environmental and Occupational Regulations for the Shreveport Final Product Formulation Facility

APPENDIX E

Controls Exercised to Minimize and Control Wastes

Manufacture of the Drug Substance

Raw materials and intermediates used in the process have been tested for compatibility with a wide range of materials used in construction. This ensures that appropriate materials have been chosen for all direct contact and sealing duties to prevent failure of equipment, instruments or piping which could lead to uncontrolled emissions.

Organic solvents are recovered by distillation, wherever possible, for reuse in the process. These distillations are carefully controlled by temperature to minimize the amount of material remaining in the product. Recovery of solvents takes place in several stages of the process, as indicated in the confidential appendix provided in this section.

Where high vacuum distillations are carried out to purify intermediates in the synthesis, then the waste residues are redissolved in an appropriate solvent to give a liquid stream suitable for incineration. This avoids the need to dispose of these waste residues by landfill.

Where volatile solvents are employed, refrigerant condensers are installed to minimize emissions of volatile organic compounds to atmosphere. Vent temperature transmitters are installed where appropriate to monitor and ensure refrigerant supply.

Scrubbers are used to reduce emissions to atmosphere, and these are detailed in the confidential appendix provided in this section. The scrubber liquor is replaced as necessary to maintain efficiency.

Aqueous wastes are monitored, using pH and visual checks, to ensure that organic material is not lost to aqueous effluent. Aqueous wastes are neutralized before disposal.

The possibility of particulate emission at the final stage is minimized by the use of a balanced heating and ventilation system which maintains an appropriate differential pressure in the relevant areas. Incoming and exhausted airs are filtered. In order to minimize release of particulate material during milling/casking operations absolute filter units are used. The exhaust passes through filters rated at 99.997% efficient in an EU 13 grading, before going to atmosphere.

Manufacturer of the Drug Product

The manufacture of the drug product consists of blending the drug substance with other dry, inactive powders and filling capsules with the blended material. Equipment and materials of construction have been chosen for all processsing steps to minimize particulate emisssion and maximize cleanability.

Cleaning wastes are minimal and would primarily consist of purified water and any residual product. IPA is used in the final cleaning step and waste would be limited to fugitive emissions. Cleaning wastes are discharged to the process sewer for treatment by the city.

The amount of particulate emission is low and is minimized by the use of a balanced heating, ventilation, and air conditioning (HVAC) system which maintains an appropriate differential pressure in the relevant processing areas. All processing equipment is sealed or enclosed and appropriate dust collection is provided as required. Supply and exhaust air flows in the HVAC systems are filtered by prefilters and 99.997% HEPA filters. All dust collection is filtered in bag houses prior to exhausting to atomsphere. Used filters and collected particulate are disposed of in an approved industrial landfill.

Process rejects are evaluated and incinerated when required.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020632

PHARMACOLOGY REVIEW(S)

HESS

JUN 16 1997

NDA 20-632

Date: June 12,1997

Pharmaceutical: Meridia capsules; sibutramine hydrochloride monohydrate; BTS 54 524.

Sponsor: Knoll Pharmaceutical Company
North Mount Olive, New Jersey 07828

Review Division: Division of Endocrine and Metabolic Drug Products, HFD-510.

Consultant Reviewer:

Dr. Joseph F. Contrera
FDA/CDER Office of Testing and Research, HFD-900
Office of Pharmaceutical Sciences
CDER Expert Reviewer for Pharmaceutical Neurotoxicology

Previous Pharmacology/Toxicology Reviews:

Division of Neuropharmacological Drug Products (HFD-120) pharmacologist reviews of January 22, 1986, February 19, 1986 and October 12, 1989. Neuropharmacology, ADME and 4 week toxicity studies in rats and dogs were evaluated by Dr. Barry Rosloff.

Consultant review (by J. F. Contrera) of June 13, 1996 of volumes 1.40-1.45 and submission of April 8, 1996.

SUBMISSIONS REVIEWED

Submission received at CDER on 9/24/96. Studies BL96024 and BL96025 that further evaluate the neurotoxic potential of sibutramine compared to fenfluramine.

INTRODUCTION

In this review, the capacity of a compound to significantly alter brain neurotransmitter biomarkers was used as a preliminary indicator of neurotoxic potential. These biomarkers include: a) a reduction in brain 5HT (serotonin), DA (dopamine) or NE (norepinephrine) levels with particular attention to effects that persist for extended periods (weeks-months) after cessation of drug treatment, b) a reduction in the number of 5HT uptake sites

in the brain. Depletion of brain neurotransmitter that persists after cessation of drug treatment may be associated with axonal degeneration in animals. Although alterations in these biomarkers alone are not sufficient proof of neurotoxicity, reference neurotoxins such as 5,7-dihydroxytryptamine (5,7 DHT), p-chloroamphetamine (PCA), methylenedioxymethamphetamine (MDMA) and DSP-4 which interact with brain 5HT, DA and NE neurons respectively, profoundly affect these biomarkers.

STUDY BL96025 OBJECTIVES.

I. To compare the effects of d-fenfluramine or sibutramine on the number of 5HT reuptake sites in rat brain.

II. Protection Study: To evaluate the ability of fluoxetine or sibutramine to antagonize the effects of d-fenfluramine 5HT reuptake sites.

METHODS

Sprague-Dawley rats were treated with test compounds administered i.p. twice daily for four days. In protection studies rats received fluoxetine or sibutramine 1 hour prior to d-fenfluramine. The 4 day drug treatment was followed by a 14 day recovery period after which animals were sacrificed.

The brains were divided into frontal cortical, hippocampal and striatal regions and membrane suspensions were prepared. 5HT binding was evaluated employing tritiated paroxetine (a selective 5HT reuptake site ligand).

RESULTS

I. Effects on the Number of Brain 5HT Reuptake Sites

Sibutramine: Treatment of rats with up to 9 mg/kg sibutramine (approximately 3 times the ED50 for inhibition of food intake) had no effect on the number or affinity of 5HT reuptake sites in any brain region (Fig. 1).

D-fenfluramine: In contrast to sibutramine, d-fenfluramine at a dose equivalent to 3 times the ED50 for inhibition of food intake (3 mg/kg) produced a significant decrease in the number of 5HT reuptake sites (Fig. 1). D-fenfluramine produced a dose related decrease in the number of 5HT reuptake sites (Fig. 2) which is consistent with published reports.

Fluoxetine: Administration of fluoxetine at 10 mg/kg had no effect on the number or affinity of 5HT reuptake sites in any brain region (Fig. 3).

II. Protection Study

As reported in the literature, pretreatment with fluoxetine, a compound that selectively blocks the reuptake of 5HT by neurons, prevented the reduction in 5HT reuptake sites produced by 10 mg/kg d-fenfluramine (Fig. 3,4). Fluoxetine therefore protects the neuron from effects of d-fenfluramine. Similarly, pretreatment of rats with 9 mg/kg sibutramine also prevented most of the reduction in 5HT reuptake sites produced by 10 mg/kg d-fenfluramine.

STUDY BL96025 CONCLUSIONS

Sibutramine at up to 9 mg/kg/day and fluoxetine at 10 mg/kg/day do not produce any reduction in the number of brain 5HT reuptake sites. A significant dose related decrease in the number of brain 5HT reuptake sites is produced after treatment of rats with d-fenfluramine at 3 mg/kg and 10 mg/kg. The results with d-fenfluramine confirm the known ability of d-fenfluramine to produce a dose related decrease in the number of brain 5HT reuptake sites. The reduction in brain 5HT uptake sites is a characteristic of known serotonergic neurotoxins such as p-chloroamphetamine.

Sibutramine or fluoxetine pretreatment prevents the reduction in the number of 5HT reuptake sites of the neuron produced by d-fenfluramine. Sibutramine appears to function like floxetine in this respect, and is believed to "protect" the neuron by blocking d-fenfluramine uptake by 5HT transporter sites.

The effects of d-fenfluramine on brain 5HT reuptake sites are not shared by sibutramine.

STUDY BL96024 OBJECTIVES.

A. An experiment was designed to determine if subutramine has 5HT depleting properties similar to fenfluramine. Fenfluramine is known to produce a long lasting depletion of brain 5HT after acute treatment that has been viewed as a manifestation of neurotoxicity. From a regulatory point of view, a critical element of this study was the direct comparison of the extended effects of sibutramine and d-fenfluramine at equivalent anorexetic doses on the regional brain levels of 5HT and 5HIAA. Comparisons were also made with fluoxetine, which like sibutramine and fenfluramine, also blocks the reuptake of 5HT.

B. Effects of pretreatment with fluoxetine or sibutramine on d-fenfluramine induced changes in brain 5HT levels.

Methods

A. Sprague-Dawley rats were treated with test compounds administered i.p. twice daily for four days. Animals were sacrificed after 14 days with no treatment and the concentration of 5HT and 5HIAA were determined in the frontal cortex, striatum and hippocampus.

B. Drug Combination Studies. Sibutramine 9 mg/kg was administered p.o. twice daily for four days one hour prior to twice daily dosing with d-fenfluramine, 10 mg/kg/day p.o. for four days. In the fluoxetine combination experiment, 10 mg/kg/day fluoxetine was administered i.p. one hour prior to d-fenfluramine treatment.

Animals were sacrificed after 14 days without drug treatment and the levels of 5HT and 5HIAA were measured in the frontal cortex, striatum and hippocampus.

RESULTS

A. Treatment with 10 mg/kg/day po of d-fenfluramine for four days resulted in a statistically significant decrease in the level of 5HT of greater than 55% in the frontal cortex, hippocampus and hypothalmus after 14 days without drug treatment. Equivalent reductions in regional brain 5HIAA were also observed (Fig. 5,6).

Treatment with 9 mg/kg/day po of sibutramine for four days produced no decrease in 5HT in any brain areas and produced an increase in 5HT in the hippocampus and a 30% increase in the level of 5HIAA in the dorsal raphe (Fig. 7).

B. The combined treatment of sibutramine (9 mg/kg/day) and d-fenfluramine (10 mg/kg/day) significantly antagonized the depletion of 5HT and 5HIAA that is produced by d-fenfluramine (Fig. 8,9,10). In the presence of sibutramine, d-fenfluramine did not produce any depletion in brain 5HT and 5HIAA.

The combined treatment of fluoxetine (10 mg/kg/day) and d-fenfluramine (10 mg/kg/day) also significantly antagonized the depletion of 5HT and 5HIAA that is produced by d-fenfluramine (Fig. 11,12,13). The effects of fluoxetine on the 5HT and 5HIAA depleting effects of d-fenfluramine may be more potent than sibutramine. Fluoxetine co-treatment produced a reversal in the depleting effect of d-fenfluramine on 5HT and 5HIAA levels in the striatum and hippocampus and resulted in a statistically significant increase in 5HT and 5HIAA in these areas.

STUDY BL96024 CONCLUSIONS

Treatment of rats with sibutramine (9 mg/kg/day) for four days followed by 14 days without drug treatment did not result in a reduction in brain 5HT or 5HIAA. Similar treatment of rats with d-fenfluramine (10 mg/kg/day) resulted in significant decreases in 5HT and 5HIAA in the frontal cortex, hippocampus and hypothalamus. Long term depletion of brain 5HT is associated with p-chloroamphetamine and similar neurotoxic agents and was an issue of concern for d-fenfluramine. The 5HT depleting effect of d-fenfluramine is believed to require an interaction with the neuronal 5HT transporter and results in the depletion of neuronal 5HT due to a release of intracellular 5HT. The results of this experiment indicate that sibutramine does not produce 5HT depletion and suggest that sibutramine, in contrast to d-fenfluramine, does not induce the release of neuronal 5HT.

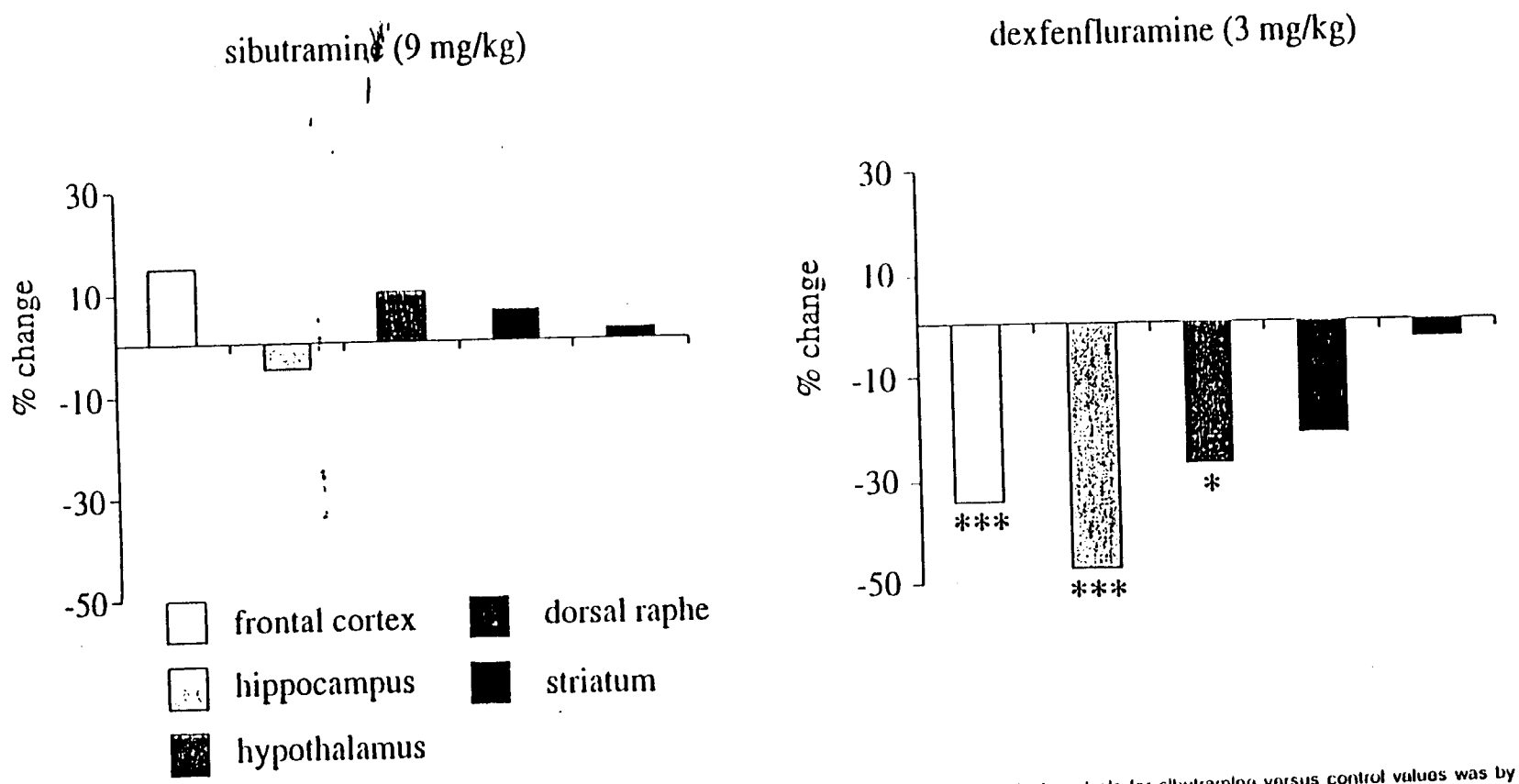
The selective 5HT uptake antagonist fluoxetine has been shown to block the uptake of d-fenfluramine and its interaction with the 5HT transporter, antagonizing the 5HT depleting effect of d-fenfluramine. Fluoxetine antagonism of d-fenfluramine induced 5HT depletion was confirmed in this report. In this regard sibutramine was found to be similar to fluoxetine. As was the case with fluoxetine, the combined treatment of sibutramine with d-fenfluramine effectively blocked the 5HT and 5HIAA depleting effects of d-fenfluramine. This observation supports the conclusion that sibutramine, like fluoxetine, may be functioning as a 5HT uptake inhibitor, blocking the uptake of d-fenfluramine into the neuron and preventing the release and depletion of 5HT.

In summary, the results of these studies support the conclusion that sibutramine inhibits the uptake of 5HT (serotonin) at the 5HT transporter site of the neuron in a manner analogous to fluoxetine. Sibutramine does not produce the persistent depletion of brain 5HT or the reduction in 5HT uptake sites that are characteristic of d-fenfluramine.

Joseph F. Contrera, Ph.D.
Associate Director, OTR

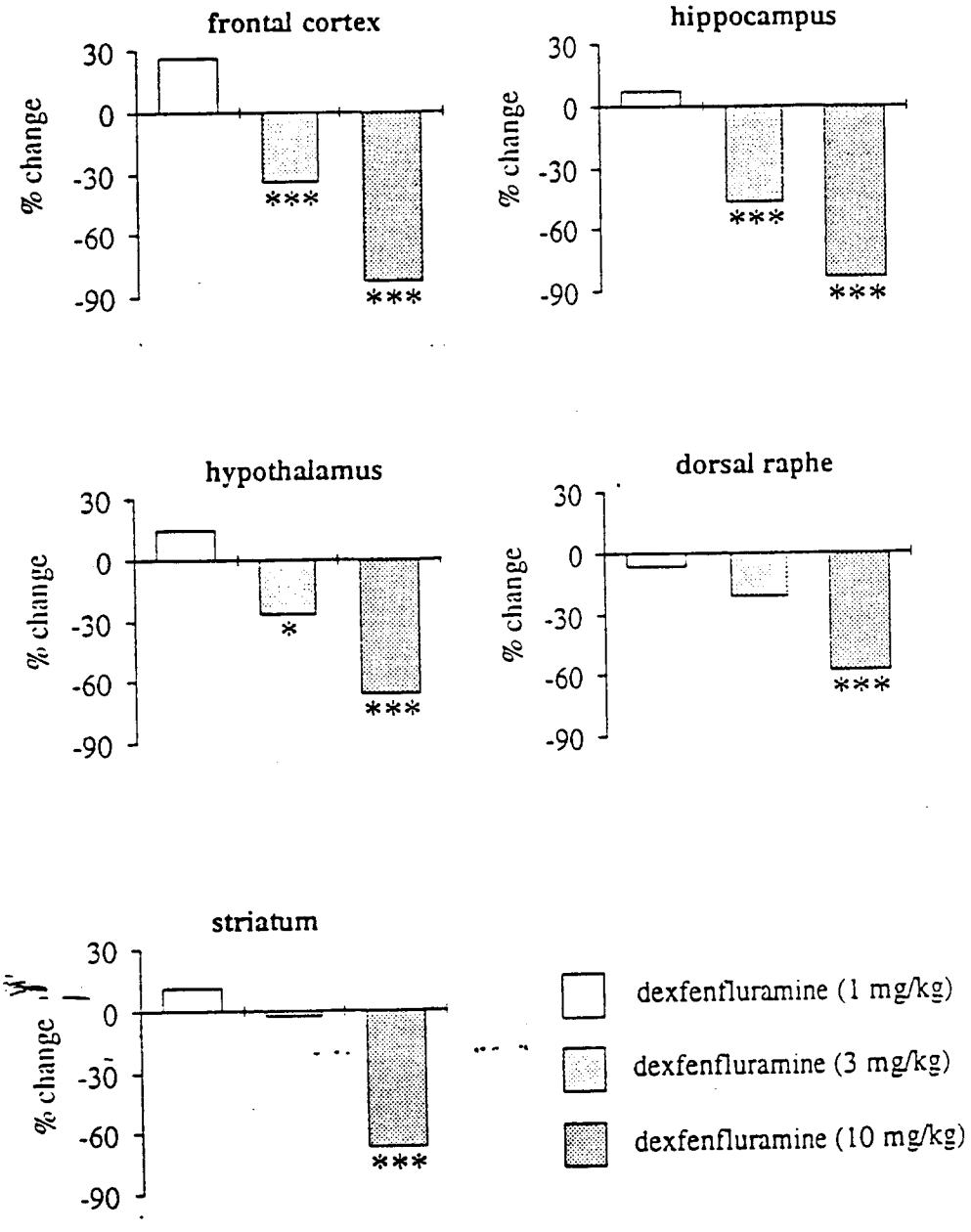
cc: NDA Arch
HFD-510/Div File
HFD-510/DHertig/EColman

FIGURE Effect of sibutramine and dexfenfluramine at doses equivalent to 3 times the ED_{50} to reduce food intake on the number of 5-HT reuptake sites labelled with [^{3}H]paroxetine.



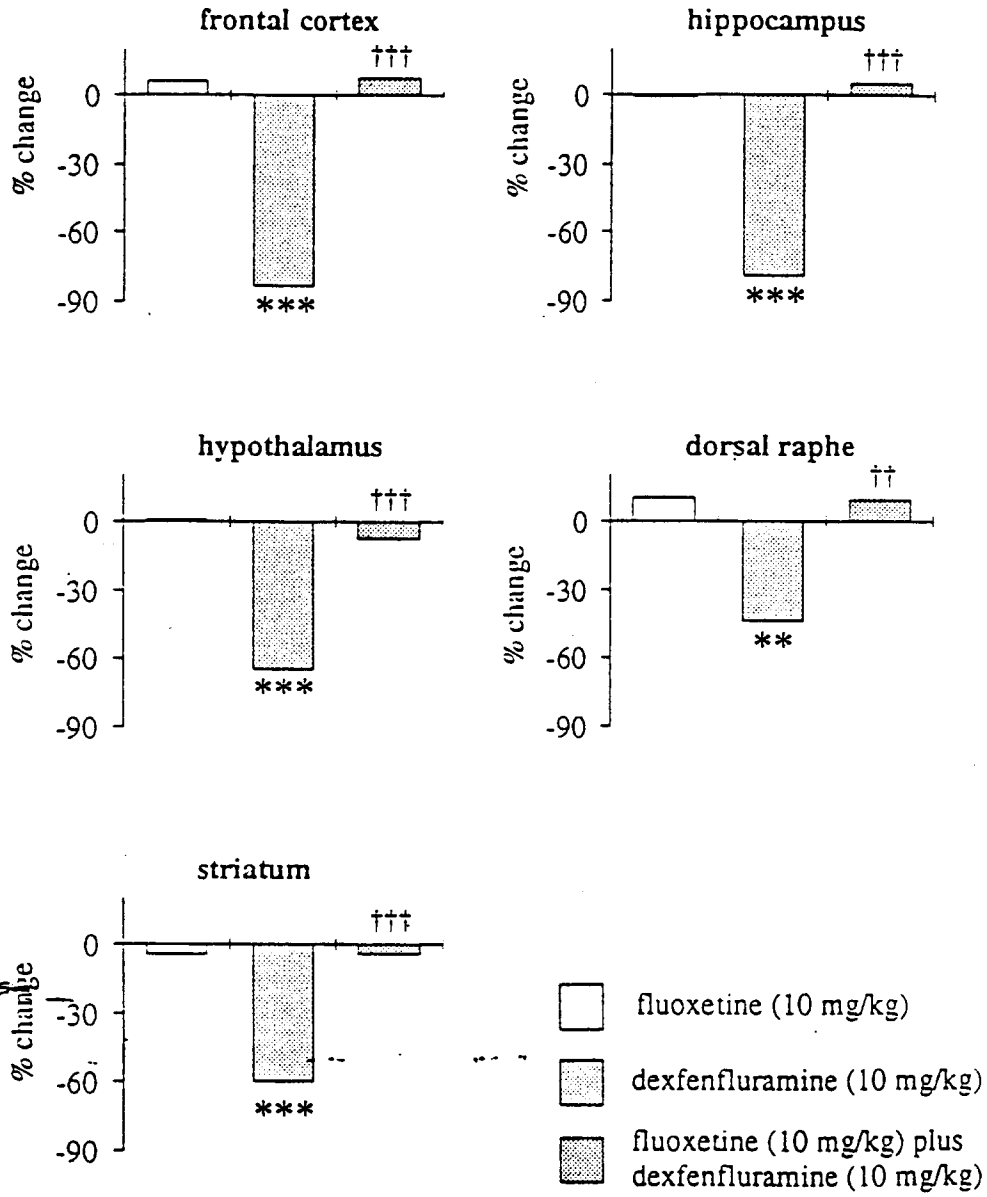
Data are mean % change from control values where control = 100% (data taken from Tables 1 and 2, n = 6-10). Statistical analysis for sibutramine versus control values was by two-way ANOVA; for dexfenfluramine versus control values, two-way ANOVA followed by Williams' test * $p < 0.05$, *** $p < 0.001$.

FIGURE 2 Effect of dexfenfluramine (1, 3 and 10 mg/kg, po) on the number of 5-HT reuptake sites labelled with [^{3}H]paroxetine



Data are mean % change from control values where control = 100% n = 5-8, Table 2. * $p < 0.05$, *** $p < 0.001$, two-way ANOVA followed by Williams' test.

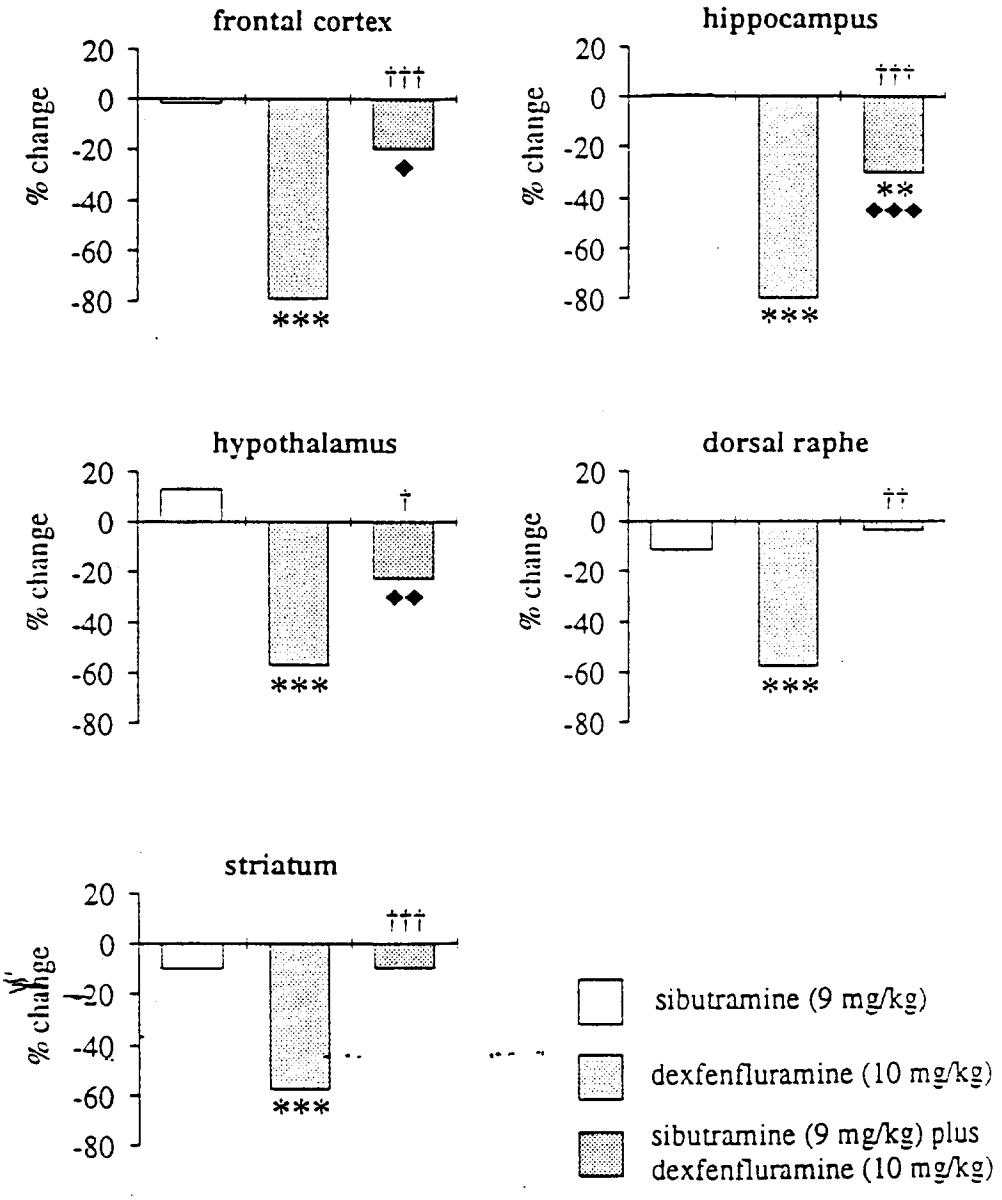
FIGURE 3 Effect of fluoxetine and dexfenfluramine both alone and in combination on the number of 5-HT reuptake sites labelled with [^{3}H]paroxetine in various regions of rat brain



Data are mean % change from control where control = 100% n = 7-10 Table 3. For comparisons with control data **p<0.01, ***p<0.001, two-way ANOVA followed by Dunnett's test. For interaction between combined drugs compared with dexfenfluramine alone ††p<0.01, †††p<0.001, multiple t-test.

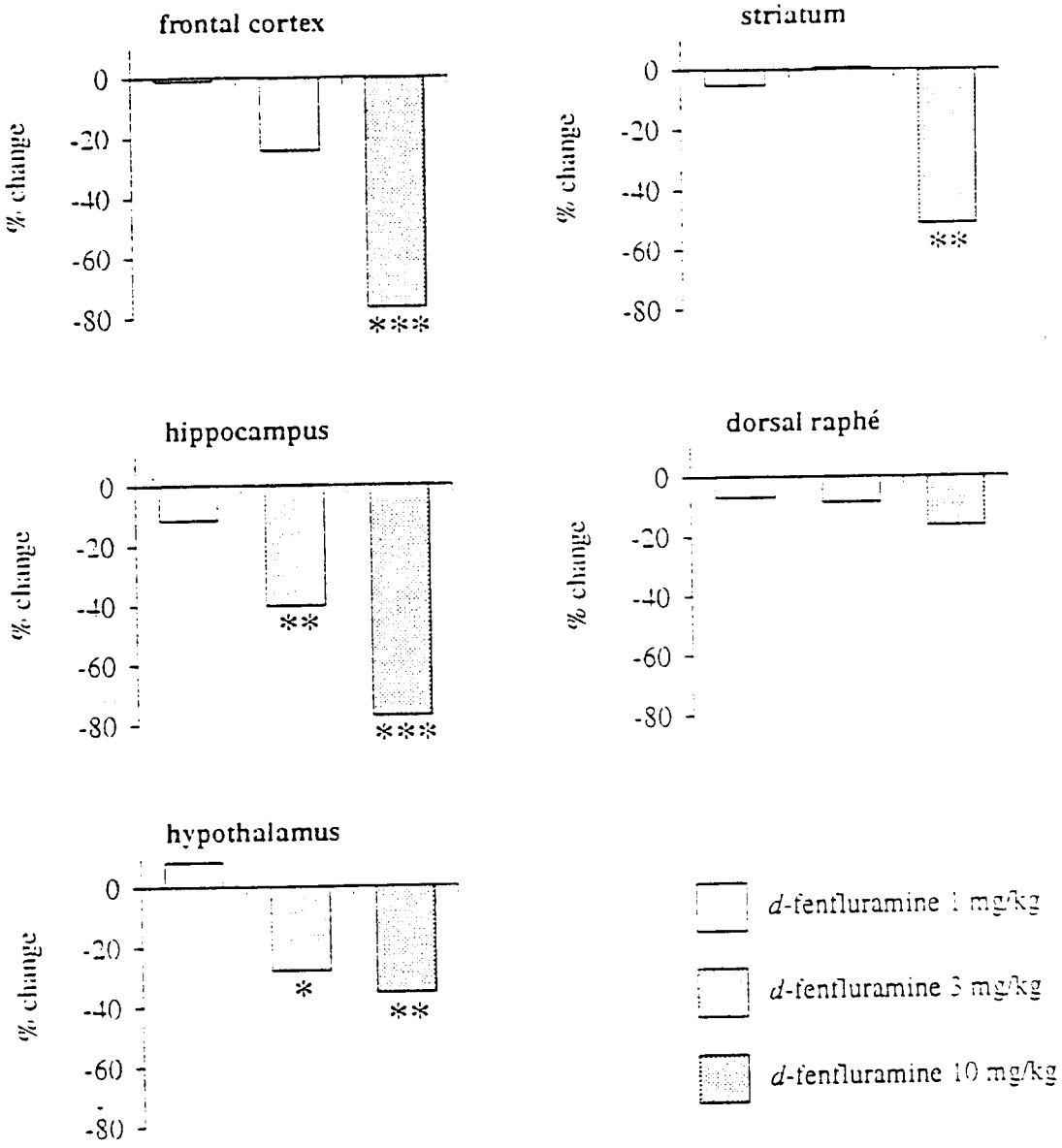
4

FIGURE 4 Effect of sibutramine and dexfenfluramine both alone and in combination on the number of 5-HT reuptake sites labelled with [^{3}H]paroxetine in various regions of rat brain



Data are mean % change from control where control = 100% n = 6-10 Table 4. For comparisons with control data **p<0.01, ***p<0.001, two-way ANOVA followed by Dunnett's test. For interaction between combined drugs compared with dexfenfluramine alone †p<0.05, ††p<0.01, †††p<0.001, multiple t-test. For comparison of sibutramine and dexfenfluramine with sibutramine alone ◆ p<0.05, ◆◆ p<0.01, ◆◆◆ p<0.001, multiple t-test.

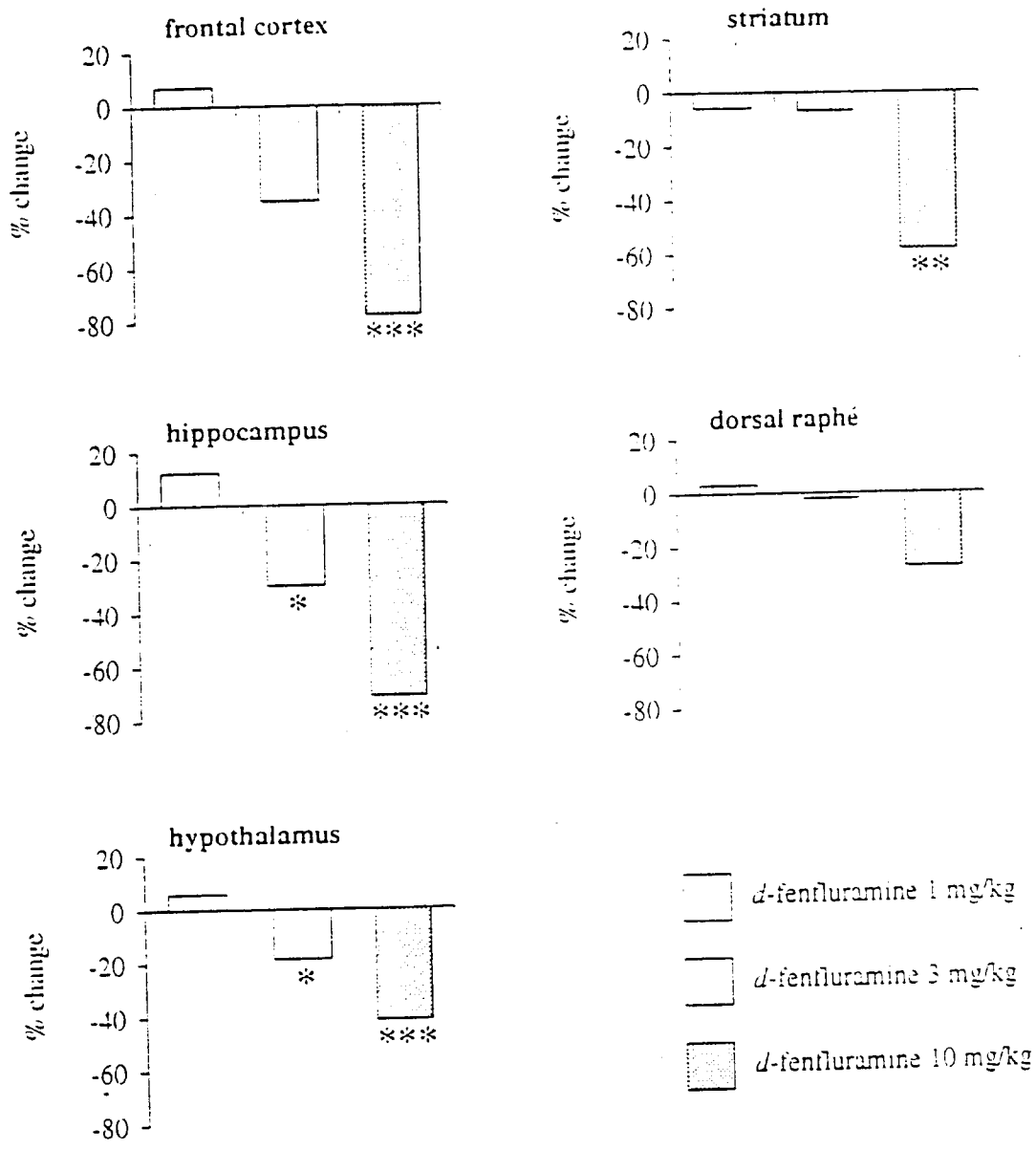
FIGURE 5 Effect of four days (twice daily) administration of d-fenfluramine (1, 3 and 10 mg/kg, po) on 5-HT levels in selected rat brain areas, measured fourteen days after cessation of treatment



Data are mean % change from control values where control = 100%. n = 8. * p<0.05, ** p<0.01, *** p<0.001 one-way ANOVA followed by William's test (Tables 2 and 12).

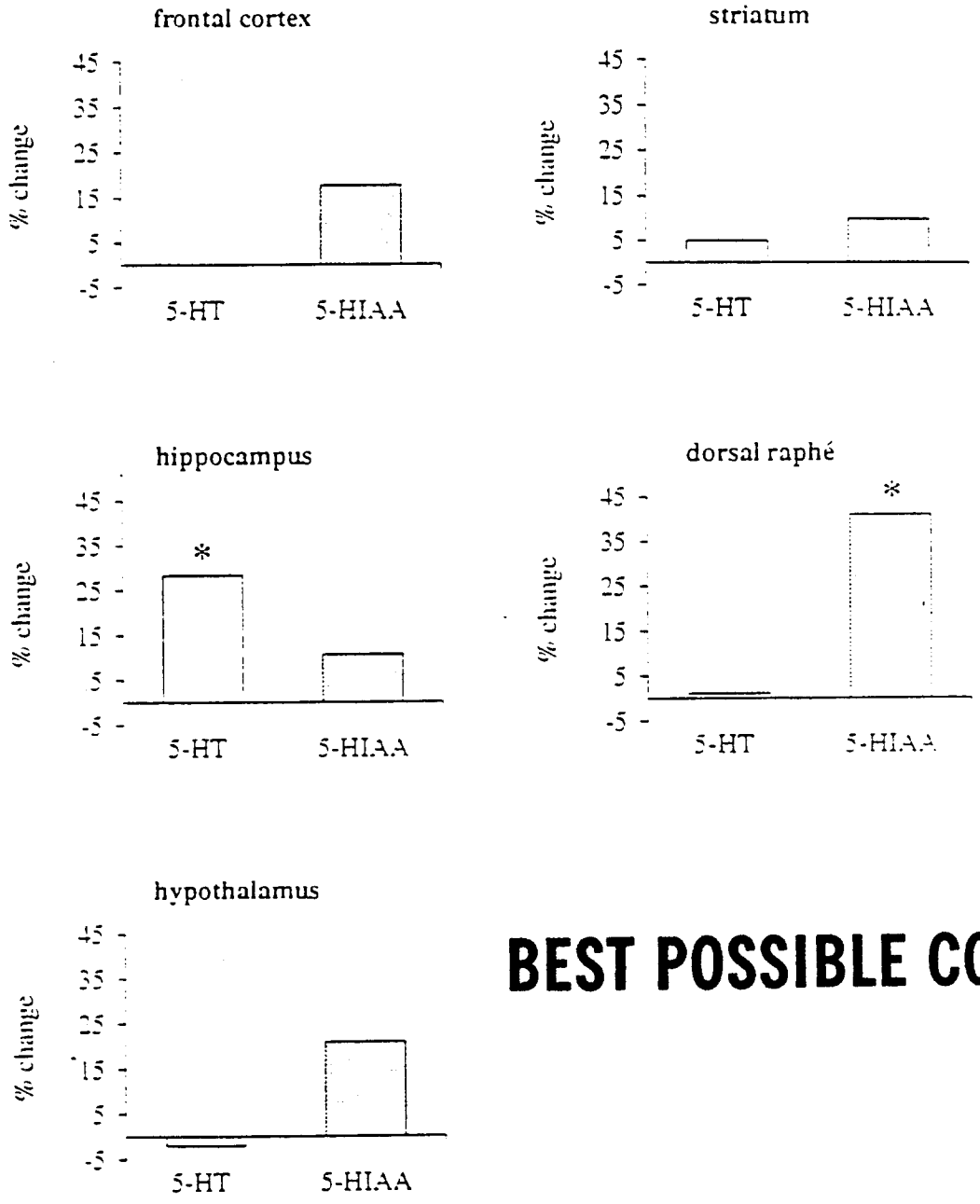
6

FIGURE 6 Effect of four days, twice daily, administration of *d*-fenfluramine (1, 3 and 10 mg/kg, po) on 5-HIAA levels in selected rat brain areas, measured fourteen days after cessation of treatment



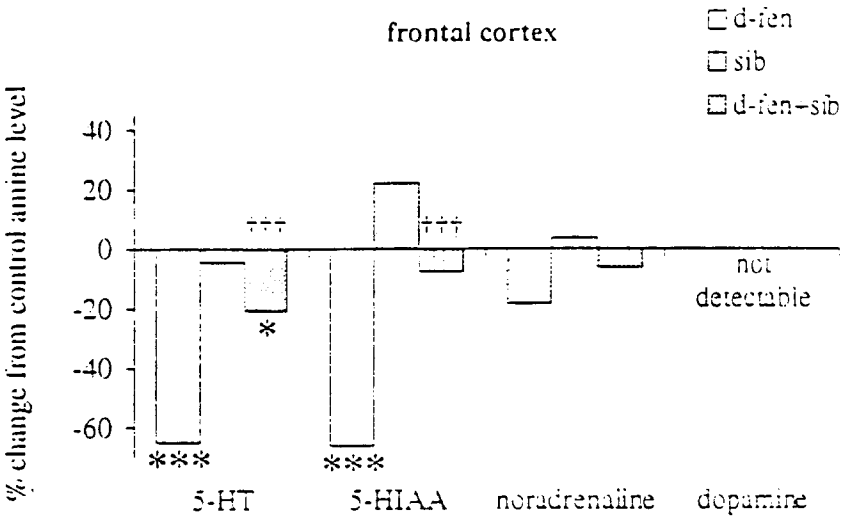
Data are mean % change from control values where control = 100%, n = 8. * p<0.05, ** p<0.01, *** p<0.001 one-way ANOVA followed by William's test (Tables 2 and 12).

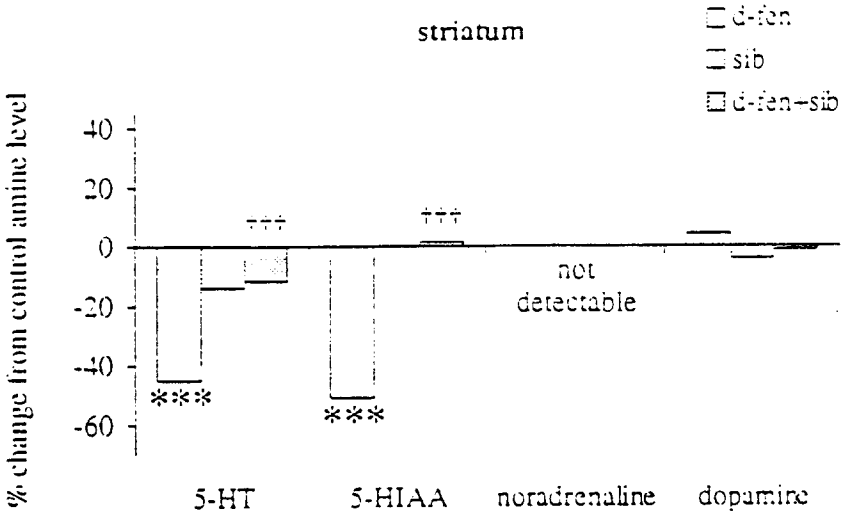
FIGURE 7 Effect of four days (twice daily) administration of sibutramine (9 mg/kg, po) on 5-HT and 5-HIAA levels in selected rat brain areas, measured fourteen days after cessation of treatment



Data are mean % change from control where control = 100%. n = 9-10 (Table 13) in all cases, except for frontal cortex where n = 20 (Table 15, data combined from experiments 2 and 2a). * $p<0.05$, one-way ANOVA followed by Dunnett's test (Table 3). Combined analysis of experiment 2 with 2a for the frontal cortex was by two-way ANOVA with treatment and experiment as factors, followed by Dunnett's test; $p>0.05$ for both 5-HT and 5-HIAA (Table 5).

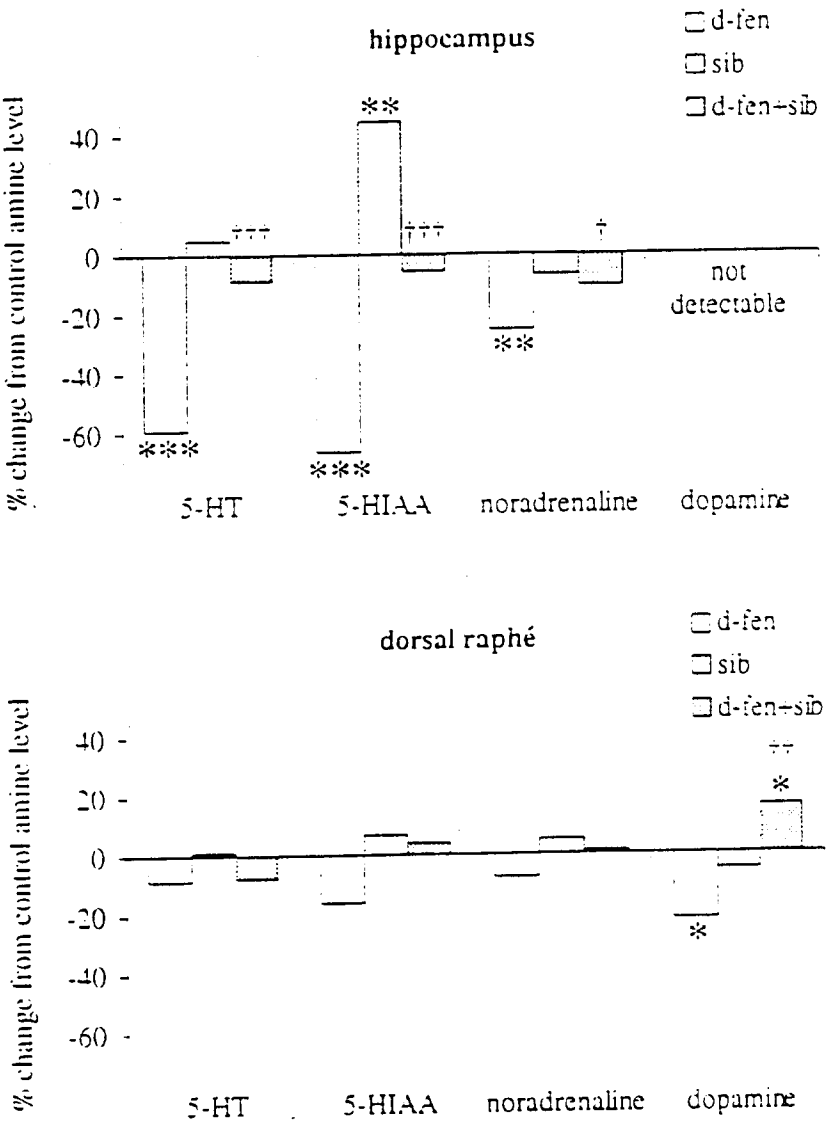
FIGURE 8 Effect of four days (twice daily) administration of d-fenfluramine (10 mg/kg, po) both alone and in combination with sibutramine (9 mg/kg,po) on amine levels in rat frontal cortex and striatum, measured fourteen days after cessation of treatment





Data are mean % change from control where control = 100%, n = 18 for 5-HT and 5-HIAA, (Table 21), n = 10 for dopamine and noradrenaline (Table 19). sib = sibutramine, d-fen = d-fenfluramine. For comparisons with control data, 5-HT and 5-HIAA, * $p<0.05$, *** $p<0.001$, two-way ANOVA followed by Dunnett's test (Table 11), noradrenaline and dopamine, $p>0.05$ one-way ANOVA followed by Dunnett's test (Table 9). Interaction between drug treatments, ††† $p<0.001$, multiple t-test on ratio of effects (Tables 9 and 11).

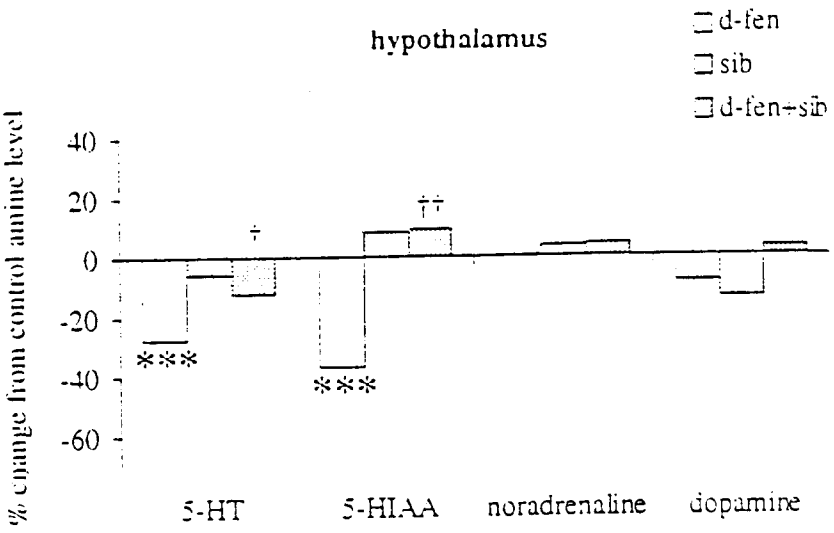
FIGURE 9 Effect of four days (twice daily) administration of d-fenfluramine (10 mg/kg, po) both alone and in combination with sibutramine (9 mg/kg, po) on amine levels in rat hippocampus and dorsal raphe, measured fourteen days after cessation of treatment



Data are mean % change from control where control = 100%, n = 17-18 for 5-HT and 5-HIAA (Table 21), n = 9-10 for dopamine and noradrenaline (Table 19). sib = sibutramine. d-fen = d-fenfluramine. For comparisons with control data, 5-HT and 5-HIAA, *** p<0.001, two-way ANOVA followed by Dunnett's test (Table 11), noradrenaline and dopamine, * p<0.05, ** p<0.01, one-way ANOVA followed by Dunnett's test (Table 9). Interaction between drug treatments, † p<0.05, †† p<0.01, ††† p<0.001, multiple t-test on ratio of effects (Tables 9 and 11).

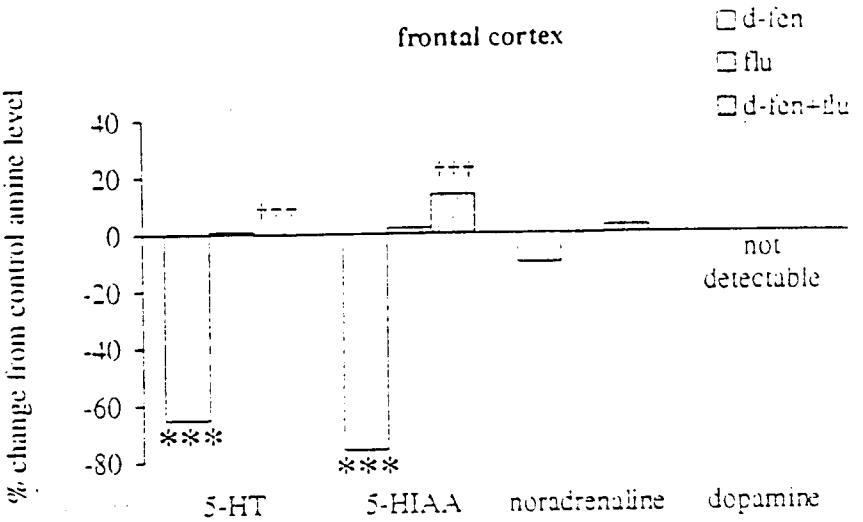
10

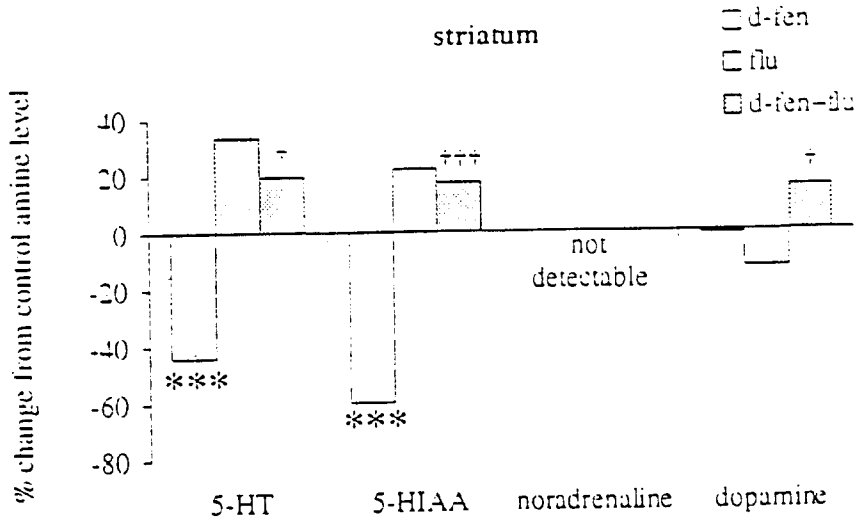
FIGURE 1 Effect of four days (twice daily) administration of d-fenfluramine (10 mg/kg, po) both alone and in combination with sibutramine (9 mg/kg, po) on amine levels in rat hypothalamus, measured fourteen days after cessation of treatment



Data are mean % change from control where control = 100%. n = 17-18 for 5-HT and 5-HIAA, (Table 21), n = 9-10 for dopamine and noradrenaline (Table 19). sib = sibutramine. d-fen = d-fenfluramine. For comparisons with control data, 5-HT and 5-HIAA, *** $p<0.001$, two-way ANOVA followed by Dunnett's test (Table 11), noradrenaline and dopamine, $p>0.05$, one-way ANOVA followed by Dunnett's test (Table 9). Interaction between drug treatments, † $p<0.05$, †† $p<0.01$, multiple t-test on ratio of effects (Tables 9 and 11).

FIGURE 11 Effect of four days (twice daily) administration of d-fenfluramine (10 mg/kg, po) both alone and in combination with fluoxetine (10 mg/kg, p) on amine levels in rat frontal cortex and striatum, measured fourteen days after cessation of treatment

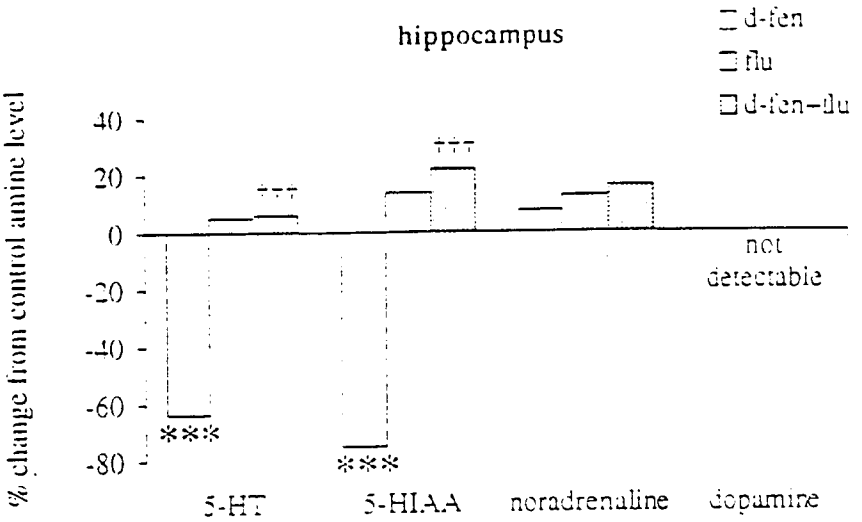


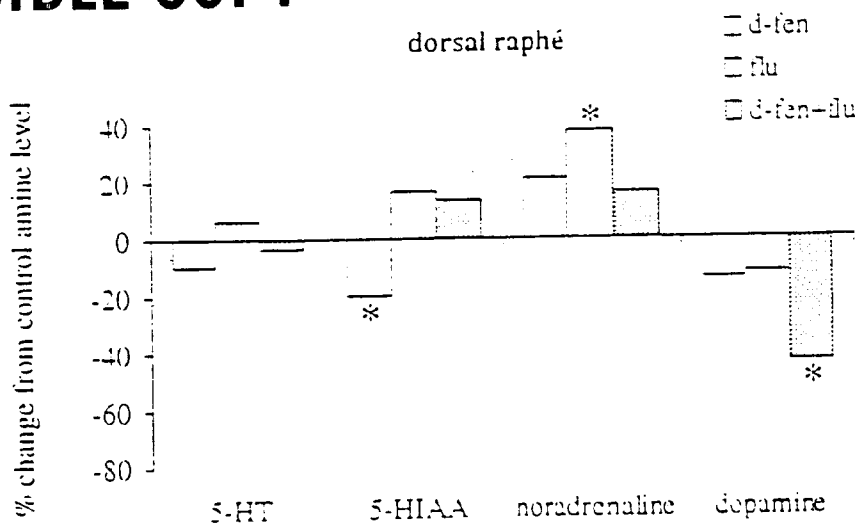


Data are mean % change from control where control = 100%, n = 17-18 for 5-HT and 5-HIAA, except for 5-HIAA in the frontal cortex where n = 14 (Table 20, 4 out of 8 samples in experiment 3 had levels which were below the limit of detection), n = 9-10 for dopamine and noradrenaline (Table 18). flu = fluoxetine. d-fen = d-fenfluramine. For comparisons with control data, 5-HT and 5-HIAA, *** $p<0.01$, two-way ANOVA followed by Dunnett's test (Table 10), noradrenaline and dopamine, $p>0.05$ one-way ANOVA followed by Dunnett's test (Table 8). Interaction between drug treatments, + $p<0.05$, +++ $p<0.001$ multiple t-test on ratio of effects (Tables 8 and 10).

12

FIGURE 9 Effect of four days (twice daily) administration of d-fenfluramine (10 mg/kg, po) both alone and in combination with fluoxetine (10 mg/kg, ip) on amine levels in rat hippocampus and dorsal raphe, measured fourteen days after cessation of treatment

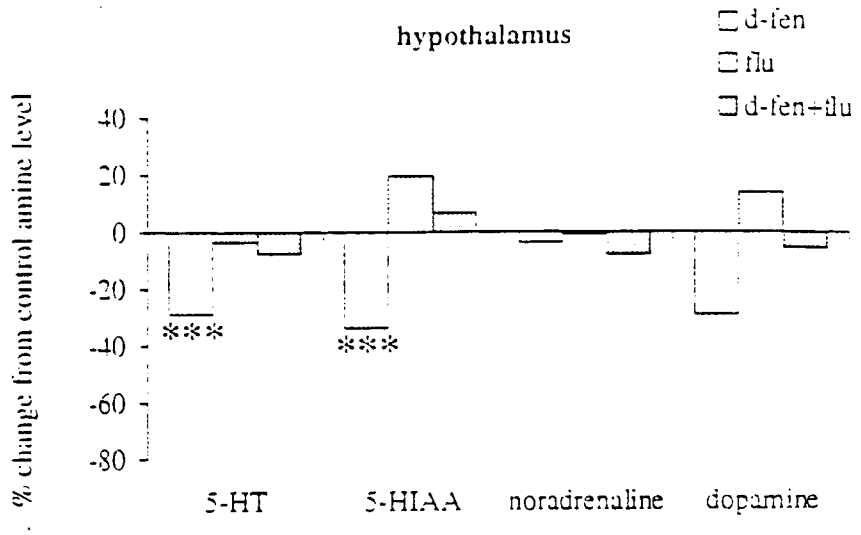




Data are mean % change from control where control = 100%. n = 17-18 for 5-HT and 5-HIAA (Table 20). n = 9-10 for dopamine and noradrenaline (Table 18). flu = fluoxetine. d-fen = d-fenfluramine. For comparisons with control data, 5-HT and 5-HIAA, * $p<0.05$, ** $p<0.01$, *** $p<0.001$, two-way ANOVA followed by Dunnett's test (Table 10), noradrenaline and dopamine, * $p<0.05$, one-way ANOVA followed by Dunnett's test (Table 8). Interaction between drug treatments, +++ $p<0.001$, multiple t-test on ratio of effects (Tables 8 and 10).

13

FIGURE 9 Effect of four days (twice daily) administration of d-fenfluramine (10 mg/kg, po) both alone and in combination with fluoxetine (10 mg/kg, po) on amine levels in rat hypothalamus, measured fourteen days after cessation of treatment



Data are mean % change from control where control = 100%, n = 18 for 5-HT and 5-HIAA (Table 20), n = 10 for dopamine and noradrenaline (Table 18). flu = fluoxetine, d-fen = d-fenfluramine. For comparisons with control data, 5-HT and 5-HIAA, *** $p<0.001$, two-way ANOVA followed by Dunnett's test (Table 10), noradrenaline and dopamine, $p>0.05$, one-way ANOVA followed by Dunnett's test (Table 8). Interaction between drug treatments, $p>0.05$, multiple t-test on ratio of effects (Tables 8 and 10).

MEMORANDUM OF CONSULTATION

Date: February 10, 1997

Between: David H. Hertig (HFD-510)

And: Baldeo K. Taneja (HFD-715)

Subject: Meridia (NDA 20-632) : Additional Statistical Analyses

Background: On the recommendation of CAC, David Hertig (Pharmacologist) asked Baldeo Taneja (Biostatistician) to conduct some additional statistical analyses for the mouse study for the NDA 20-632 (Meridia). These analyses included evaluations of hemangiomas and hemangiosarcomas (separately as well as together as a group) from all tissues with the instruction that animals with multiple tumors should be considered as one tumor finding.

Statistical Analyses: There were two control groups in this study. At the request of the pharmacologist, the following 12 analyses were performed for the mouse study. These analyses were conducted by Ted Guo, Ph.D. (HFD-715).

Control Groups	Sex	Hemangioma and Hemangiosarcoma Separately	Hemangioma and Hemangiosarcoma Together as a group
Control 1	Male	Analysis 1 (pages 1 - 3)	Analysis 7 (pages 20 - 22)
	Female	Analysis 2 (pages 4 - 6)	Analysis 8 (pages 23 - 25)
Control 2	Male	Analysis 3 (pages 7 - 9)	Analysis 9 (pages 26 - 28)
	Female	Analysis 4 (pages 10 - 12)	Analysis 10 (pages 29 - 31)
Control 1+ Control 2	Male	Analysis 5 (pages 13 - 15)	Analysis 11 (pages 32 - 34)
	Female	Analysis 6 (pages 16 - 19)	Analysis 12 (pages 35 - 38)

Statistical Results: The following Table gives all the appropriate p-values. All the p-values are non-significant.

Control Groups	Sex	Separate		Hemangioma and Hemangiosarcoma Together as a group
		Hemangioma	Hemangiosarcoma	
Control 1	Male	0.505	0.500	0.446
	Female	0.259	0.421	0.248
Control 2	Male	0.280	0.590	0.392
	Female	0.346	0.805	0.601
Control 1+Control 2	Male	0.361	0.681	0.538
	Female	0.259	0.671	0.405

Baldeo K. Taneja, Ph.D.
Mathematical Statistician

cc:
Arch. NDA 20-632
HFD-510/Hertig/CSO/Division File
HFD-715/Taneja/Marticello/Lin/Nevius/Division File/Chron.

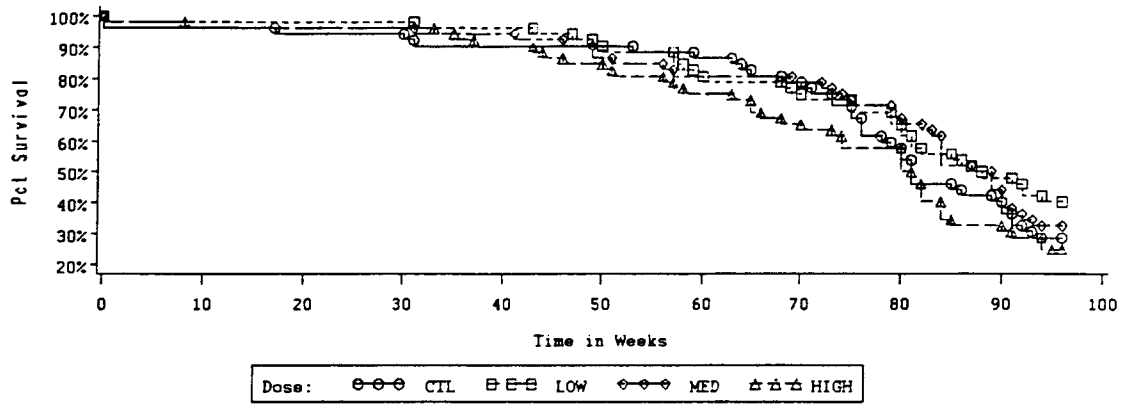
2/11/97

APPEARS THIS WAY
ON ORIGINAL

Carcinogenicity Study

Kaplan-Meier Survival Function

Animal: Mouse
Sex: Male



Dose: CTL LOW MED HIGH

Data Source: c:\b\XMICE2.TXT

Graph saved at c:\b\KM_Mou_M.sc2

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (15:46)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
*COMBINED (OHM		)*HEMANGIOMA* (HMG		) IN	IN 53-78		0.505	0.425	0.439
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
		Tumor rate: 2%		in CTL -	Total				
*COMBINED (OHS		)*HEMANGIOSARC(HMS		) MX	IN 79-95		0.522	0.487	0.500
					IN 79-95				
					FA 68				
					FA 68				
					FA 70				
					FA 70				
					FA 87				
					FA 87				
		Tumor rate: 4%		in CTL -	Total				
*OTHER ORG(OTH		)*OTHER TUMORS(OTH		) MX	IN 0-52		0.688	0.689	0.691
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 43				
					FA 43				
					FA 44				
					FA 44				
					FA 46				
					FA 46				
					FA 50				
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					FA 63				
					FA 63				
					FA 66				
					FA 66				
					FA 68				
					FA 68				
					FA 69				

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (15:46)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	69					
				FA	70					
				FA	70					
				FA	73					
				FA	73					
				FA	75					
				FA	75					
				FA	76					
				FA	76					
				FA	79					
				FA	79					
				FA	80					
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				FA	91					
				FA	91					
				FA	92					
				FA	92					
				FA	93					
				FA	93					
				FA	94					
				FA	94					
				FA	96					
				FA	96					

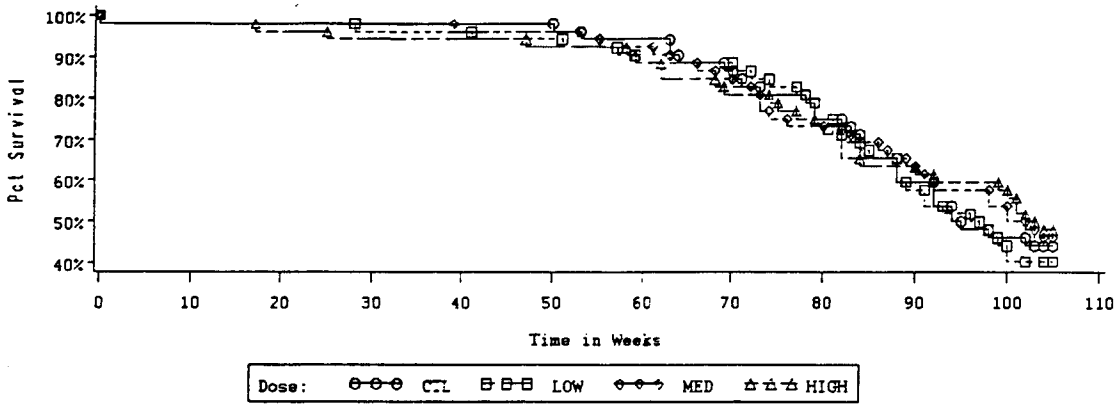
Tumor rate: 71% in CTL - Total

Page - 2 - (End of File)

Carcinogenicity Study

Kaplan-Meier Survival Function

Animal: Mouse
Sex: Female



Date Source: c:\b\XMICE2.TXT

Graph saved at c:\b\KM_Mou_F.sc2

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (16:33)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
*COMBINED (OHM		*HEMANGIOMA* (HMG		MX	IN 92-103		0.247	0.251	0.259
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 102				
					FA 102				
		Tumor rate: 2%		in CTL -	Total				
*COMBINED (OHS		*HEMANGIOSARC(HMS		MX	IN 79-91		0.426	0.407	0.421
					IN 79-91				
					FA 82				
					FA 82				
					FA 104				
					FA 104				
		Tumor rate: <1%		in CTL -	Total				
*OTHER ORG(OTH		*OTHER TUMORS(OTH		MX	IN 0-52		0.365	0.364	0.367
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-91				
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 28				
					FA 28				
					FA 41				
					FA 41				
					FA 50				
					FA 50				
					FA 53				
					FA 53				
					FA 55				
					FA 55				
					FA 57				
					FA 57				
					FA 59				
					FA 59				
					FA 63				
					FA 63				
					FA 64				
					FA 64				
					FA 68				
					FA 68				
					FA 69				
					FA 69				
					FA 71				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (16:33)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL LOW MED HIGH (0 1.25 5 20)

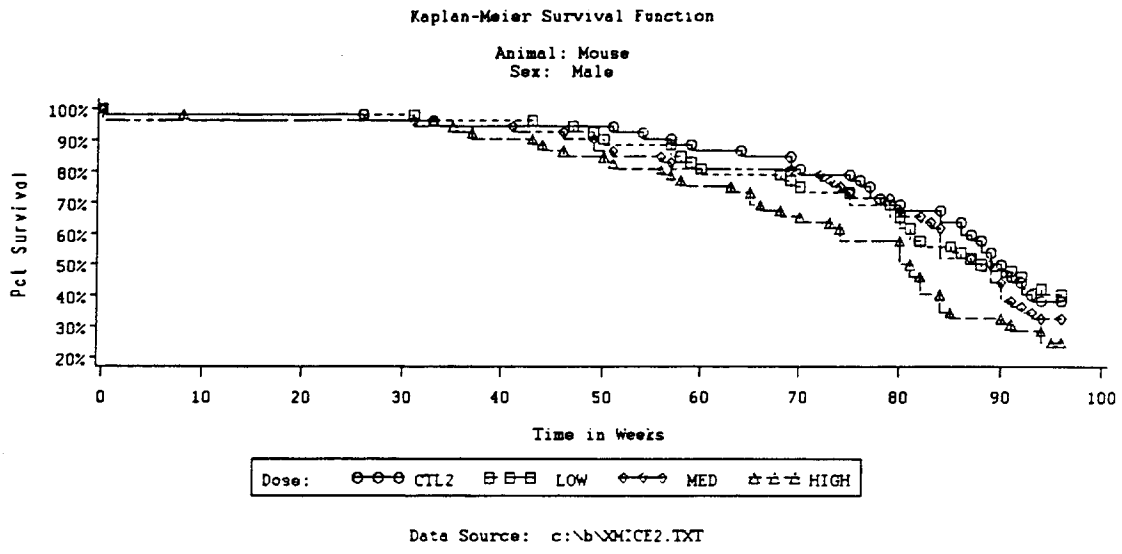
Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	71				
				FA	72				
				FA	72				
				FA	74				
				FA	74				
				FA	75				
				FA	75				
				FA	76				
				FA	76				
				FA	77				
				FA	77				
				FA	78				
				FA	78				
				FA	79				
				FA	79				
				FA	80				
				FA	80				
				FA	81				
				FA	81				
				FA	82				
				FA	82				
				FA	83				
				FA	83				
				FA	84				
				FA	84				
				FA	85				
				FA	85				
				FA	88				
				FA	88				
				FA	89				
				FA	89				
				FA	90				
				FA	90				
				FA	92				
				FA	92				
				FA	98				
				FA	98				
				FA	99				
				FA	99				
				FA	100				
				FA	100				
				FA	102				
				FA	102				

Tumor rate: 75% in CTL - Total

Page - 2 - (End of File)

Carcinogenicity Study



Data Source: c:\b\XMICE2.TXT

Graph saved at c:\b\KM_Mou_M.sc2

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (16:02)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL2 LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
*COMBINED (OHM		)*HEMANGIOMA* (HMG		) IN	IN 79-95		0.280	0.197	0.210
					IN 79-95				
					IN 96-96				
					IN 96-96				
		Tumor rate: <1%		in CTL -	Total				
*COMBINED (OHS		)*HEMANGIOSARC(HMS		) MX	IN 79-95		0.598	0.578	0.590
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 70				
					FA 70				
					FA 87				
					FA 87				
		Tumor rate: <1%		in CTL -	Total				
*OTHER ORG(OTH		)*OTHER TUMORS(OTH		) MX	IN 0-52		0.542	0.542	0.545
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 43				
					FA 43				
					FA 44				
					FA 44				
					FA 46				
					FA 46				
					FA 50				
					FA 50				
					FA 56				
					FA 56				
					FA 57				
					FA 57				
					FA 58				
					FA 58				
					FA 59				
					FA 59				
					FA 60				
					FA 60				
					FA 66				
					FA 66				
					FA 68				
					FA 68				
					FA 69				
					FA 69				
					FA 70				

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (16:02)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL2 LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	70				
				FA	73				
				FA	73				
				FA	75				
				FA	75				
				FA	76				
				FA	76				
				FA	79				
				FA	79				
				FA	80				
				FA	80				
				FA	81				
				FA	81				
				FA	82				
				FA	82				
				FA	84				
				FA	84				
				FA	87				
				FA	87				
				FA	89				
				FA	89				
				FA	90				
				FA	90				
				FA	91				
				FA	91				
				FA	93				
				FA	93				
				FA	94				
				FA	94				
				FA	96				
				FA	96				

Tumor rate: <1% in CTL - Total

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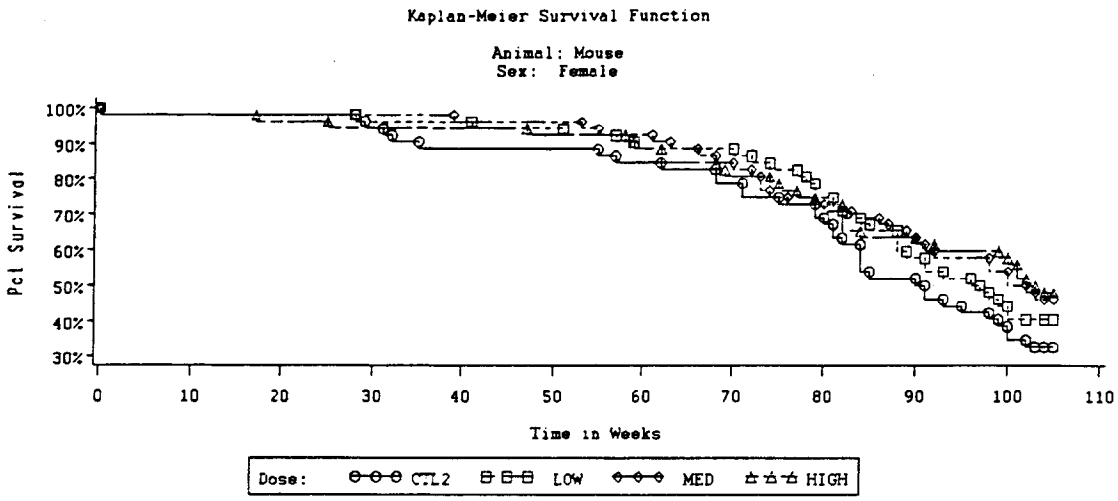
Carcinogenicity Study



Data Source: c:\b\XMICE2.TXT

Graph saved at c:\b\KM_Mou_F.sc2

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (16:36)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL2 LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
*COMBINED	(OHM	)*HEMANGIOMA*	(HMG	) MX	IN 92-103		0.339	0.337	0.346
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 102				
					FA 102				
		Tumor rate: <1%		in CTL -	Total				
*COMBINED	(OHS	)*HEMANGIOSARC	(HMS	) MX	IN 79-91		0.814	0.797	0.805
					IN 79-91				
					IN 92-103				
					IN 92-103				
					FA 82				
					FA 82				
					FA 95				
					FA 95				
					FA 104				
					FA 104				
		Tumor rate: <1%		in CTL -	Total				
*OTHER ORG	(OTH	)*OTHER TUMORS	(OTH	) MX	IN 0-52		0.276	0.275	0.277
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-91				
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 28				
					FA 28				
					FA 29				
					FA 29				
					FA 31				
					FA 31				
					FA 32				
					FA 32				
					FA 41				
					FA 41				
					FA 53				
					FA 53				
					FA 55				
					FA 55				
					FA 57				
					FA 57				
					FA 59				
					FA 59				
					FA 68				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (16:36)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL2 LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 68				
					FA 69				
					FA 69				
					FA 72				
					FA 72				
					FA 74				
					FA 74				
					FA 75				
					FA 75				
					FA 76				
					FA 76				
					FA 77				
					FA 77				
					FA 78				
					FA 78				
					FA 79				
					FA 79				
					FA 80				
					FA 80				
					FA 81				
					FA 81				
					FA 82				
					FA 82				
					FA 83				
					FA 83				
					FA 84				
					FA 84				
					FA 85				
					FA 85				
					FA 88				
					FA 88				
					FA 89				
					FA 89				
					FA 90				
					FA 90				
					FA 92				
					FA 92				
					FA 93				
					FA 93				
					FA 99				
					FA 99				
					FA 100				
					FA 100				
					FA 102				
					FA 102				

Tumor rate: <1% in CTL - Total

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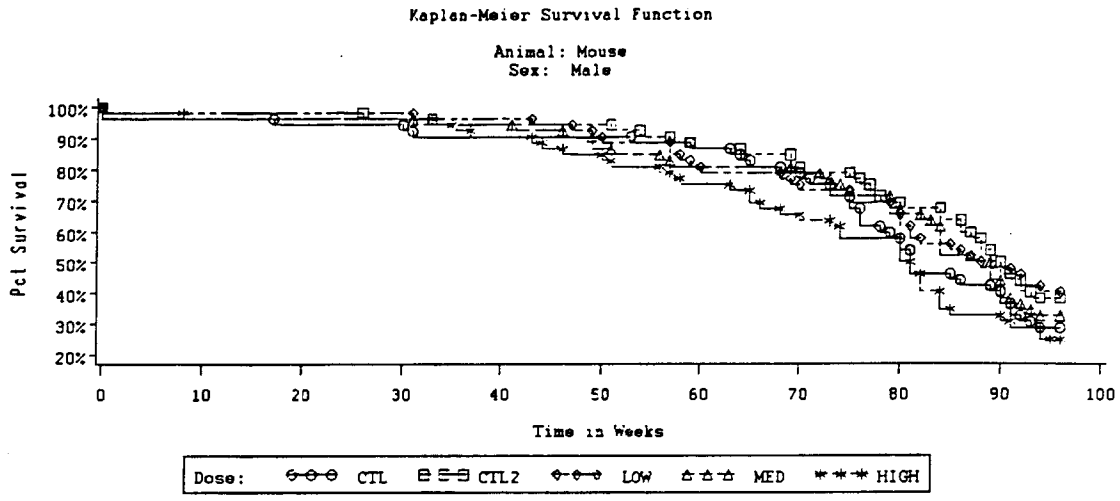
Carcinogenicity Study



Data Source: c:\b\XMICE2.TXT

Graph saved at c:\b\KM_Mou_M.sc2

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (16:27)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
*COMBINED (OHM		)*HEMANGIOMA* (HMG		) IN	IN 53-78		0.361	0.306	0.320
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
		Tumor rate: 2%		in CTL -	Total				
*COMBINED (OHS		)*HEMANGIOSARC(HMS		) MX	IN 79-95		0.682	0.672	0.681
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 68				
					FA 68				
					FA 70				
					FA 70				
					FA 87				
					FA 87				
		Tumor rate: 4%		in CTL -	Total				
*OTHER ORG(OTH		)*OTHER TUMORS(OTH		) MX	IN 0-52		0.710	0.710	0.713
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 43				
					FA 43				
					FA 44				
					FA 44				
					FA 46				
					FA 46				
					FA 50				
					FA 50				
					FA 56				
					FA 56				
					FA 57				
					FA 57				
					FA 58				
					FA 58				
					FA 59				
					FA 59				
					FA 60				
					FA 60				
					FA 63				
					FA 63				
					FA 66				

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (16:27)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	66				
				FA	68				
				FA	68				
				FA	69				
				FA	69				
				FA	70				
				FA	70				
				FA	73				
				FA	73				
				FA	75				
				FA	75				
				FA	76				
				FA	76				
				FA	79				
				FA	79				
				FA	80				
				FA	80				
				FA	81				
				FA	81				
				FA	82				
				FA	82				
				FA	84				
				FA	84				
				FA	85				
				FA	85				
				FA	86				
				FA	86				
				FA	87				
				FA	87				
				FA	89				
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				FA	90				
				FA	90				
				FA	91				
				FA	91				
				FA	92				
				FA	92				
				FA	93				
				FA	93				
				FA	94				
				FA	94				
				FA	96				
				FA	96				

Tumor rate: 71% in CTL - Total

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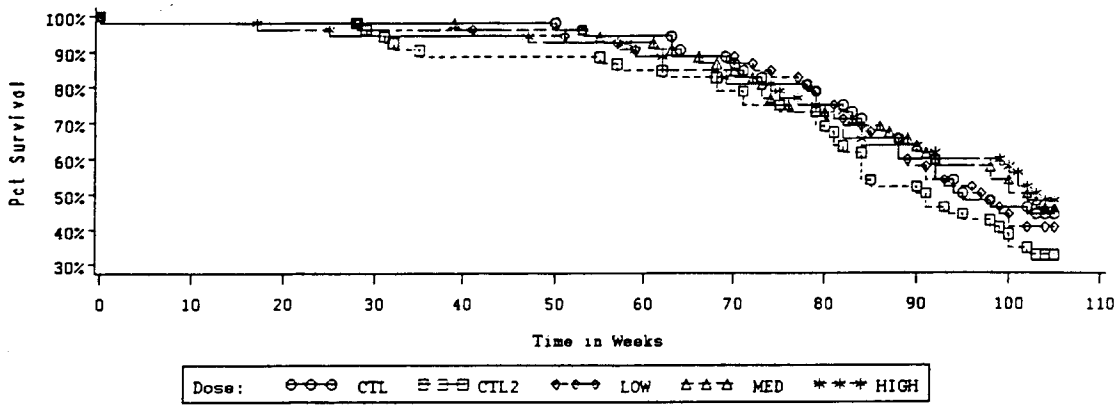
Carcinogenicity Study

Kaplan-Meier Survival Function

Animal: Mouse
Sex: Female



Data Source: c:\b\XMICE2.TXT

Graph saved at c:\b\KM_Mou_F.sc2

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (16:40)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
*COMBINED (OHM		)*HEMANGIOMA* (HMG		) MX	IN 92-103		0.244	0.251	0.259
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 102				
					FA 102				
		Tumor rate: 2%		in CTL -	Total				
*COMBINED (OHS		)*HEMANGIOSARC(HMS		) MX	IN 79-91		0.675	0.661	0.671
					IN 79-91				
					IN 92-103				
					IN 92-103				
					FA 82				
					FA 82				
					FA 95				
					FA 95				
					FA 104				
					FA 104				
		Tumor rate: <1%		in CTL -	Total				
*OTHER ORG(OTH		)*OTHER TUMORS(OTH		) MX	IN 0-52		0.360	0.360	0.362
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-91				
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 28				
					FA 28				
					FA 29				
					FA 29				
					FA 31				
					FA 31				
					FA 32				
					FA 32				
					FA 41				
					FA 41				
					FA 50				
					FA 50				
					FA 53				
					FA 53				
					FA 55				
					FA 55				
					FA 57				
					FA 57				
					FA 59				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (16:40)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA	59					
				FA	63					
				FA	63					
				FA	64					
				FA	64					
				FA	68					
				FA	68					
				FA	69					
				FA	69					
				FA	71					
				FA	71					
				FA	72					
				FA	72					
				FA	74					
				FA	74					
				FA	75					
				FA	75					
				FA	76					
				FA	76					
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				FA	85					
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				FA	89					
				FA	89					
				FA	90					
				FA	90					
				FA	92					
				FA	92					
				FA	93					
				FA	93					
				FA	98					
				FA	98					

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (16:40)
Source: c:\b\XMICE2.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

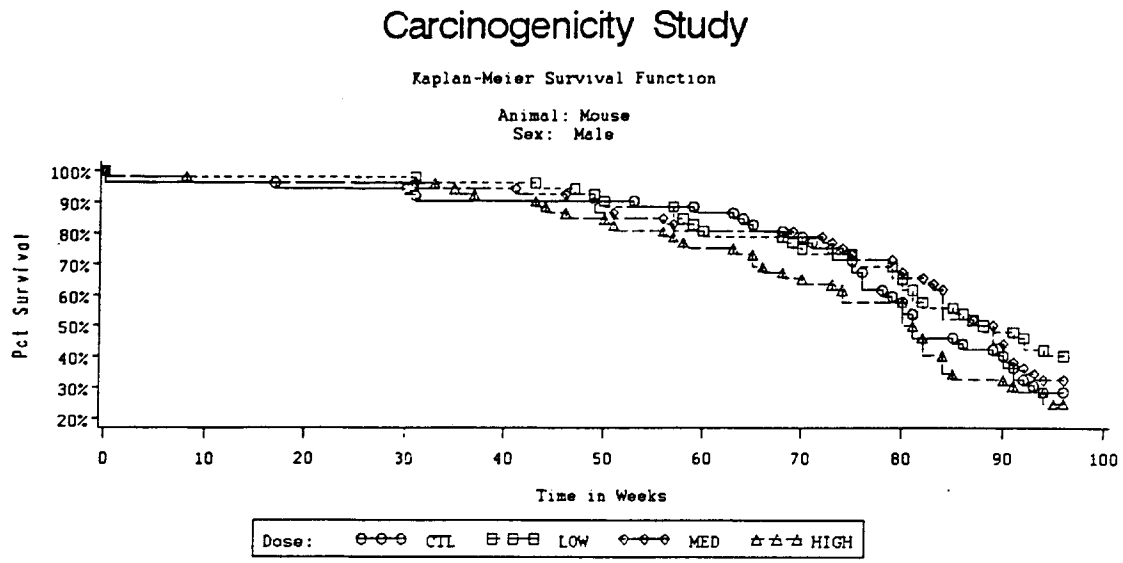
Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA	99				
				FA	99				
				FA	100				
				FA	100				
				FA	102				
				FA	102				

Tumor rate: 75% in CTL - Total

Page - 3 - (End of File)

Starting here, two tumors are combined



Data Source: c:\b\XMICE3.TXT

Graph saved at c:\b\KM_Mou_M.sc2

APPEARS THIS WAY
ON ORIGINAL

BEST POSSIBLE COPY

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (16:52)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
**ORGANS	H(OHMS)	**HEMANGIOMA	(HMGS)	MX	IN 53-78		0.455	0.437	0.446
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 68				
					FA 68				
					FA 70				
					FA 70				
					FA 87				
					FA 87				
		Tumor rate: 6%		in CTL -	Total				
*OTHER ORG	(OTH)	*OTHER TUMORS	(OTH)	MX	IN 0-52		0.688	0.689	0.691
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 43				
					FA 43				
					FA 44				
					FA 44				
					FA 46				
					FA 46				
					FA 50				
					FA 50				
					FA 56				
					FA 56				
					FA 57				
					FA 57				
					FA 58				
					FA 58				
					FA 60				
					FA 60				
					FA 63				
					FA 63				
					FA 66				
					FA 66				
					FA 68				
					FA 68				
					FA 69				
					FA 69				
					FA 70				
					FA 70				
					FA 73				

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (16:52)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
					FA 73				
					FA 75				
					FA 75				
					FA 76				
					FA 76				
					FA 79				
					FA 79				
					FA 80				
					FA 80				
					FA 81				
					FA 81				
					FA 82				
					FA 82				
					FA 84				
					FA 84				
					FA 85				
					FA 85				
					FA 86				
					FA 86				
					FA 87				
					FA 87				
					FA 89				
					FA 89				
					FA 90				
					FA 90				
					FA 91				
					FA 91				
					FA 92				
					FA 92				
					FA 93				
					FA 93				
					FA 94				
					FA 94				
					FA 96				
					FA 96				

Tumor rate: 71% in CTL - Total

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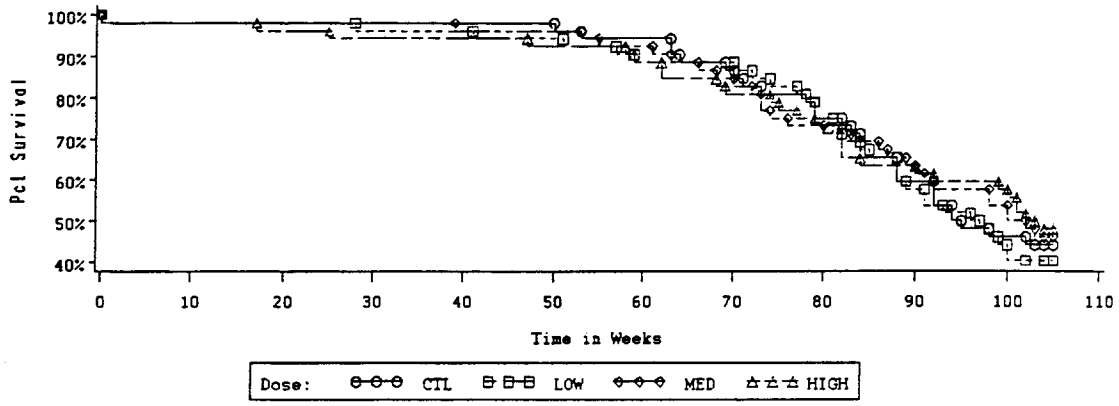
Carcinogenicity Study

Kaplan-Meier Survival Function

Animal: Mouse
Sex: Female



Data Source: c:\b\XMICE3.TXT

Graph saved at c:\b\KM_Mou_F.sc2

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (17:04)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
**ORGANS H	(OHMS)	**HEMANGIOMA	(HMGS)	MX	IN 79-91		0.237	0.241	0.248
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 82				
					FA 82				
					FA 102				
					FA 102				
					FA 104				
					FA 104				
		Tumor rate: 2%		in CTL -	Total				
*OTHER ORG	(OTH)	*OTHER TUMORS	(OTH)	MX	IN 0-52		0.365	0.364	0.367
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-91				
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 28				
					FA 28				
					FA 41				
					FA 41				
					FA 50				
					FA 50				
					FA 53				
					FA 53				
					FA 55				
					FA 55				
					FA 57				
					FA 57				
					FA 59				
					FA 59				
					FA 63				
					FA 63				
					FA 64				
					FA 64				
					FA 68				
					FA 68				
					FA 69				
					FA 69				
					FA 71				
					FA 71				
					FA 72				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (17:04)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

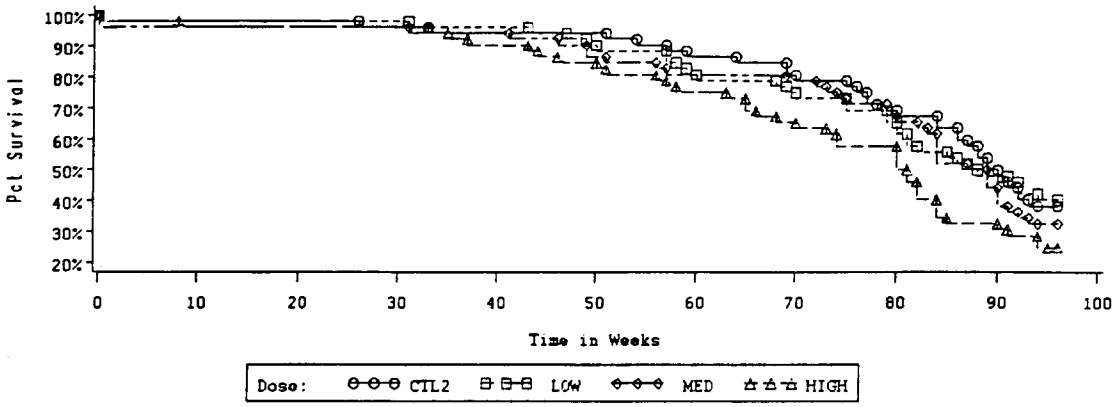
ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	72				
				FA	74				
				FA	74				
				FA	75				
				FA	75				
				FA	76				
				FA	76				
				FA	77				
				FA	77				
				FA	78				
				FA	78				
				FA	79				
				FA	79				
				FA	80				
				FA	80				
				FA	81				
				FA	81				
				FA	82				
				FA	82				
				FA	83				
				FA	83				
				FA	84				
				FA	84				
				FA	85				
				FA	85				
				FA	88				
				FA	88				
				FA	89				
				FA	89				
				FA	90				
				FA	90				
				FA	92				
				FA	92				
				FA	98				
				FA	98				
				FA	99				
				FA	99				
				FA	100				
				FA	100				
				FA	102				
				FA	102				

Tumor rate: 75% in CTL - Total

Carcinogenicity Study

Kaplan-Meier Survival Function

Animal: Mouse
Sex: Male



Data Source: c:\b\XMICE3.TXT

Graph saved at c:\b\KM_Mou_M.ec2

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 9, 1997 (17:26)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL2 LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
**ORGANS H	(OHMS)	**HEMANGIOMA	(HMGS)	MX	IN 79-95		0.403	0.382	0.392
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 70				
					FA 70				
					FA 87				
					FA 87				
		Tumor rate: <1%		in CTL -	Total				
*OTHER ORG	(OTH)	*OTHER TUMORS	(OTH)	MX	IN 0-52		0.542	0.542	0.545
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 43				
					FA 43				
					FA 44				
					FA 44				
					FA 46				
					FA 46				
					FA 50				
					FA 50				
					FA 56				
					FA 56				
					FA 57				
					FA 57				
					FA 58				
					FA 58				
					FA 59				
					FA 59				
					FA 60				
					FA 60				
					FA 66				
					FA 66				
					FA 68				
					FA 68				
					FA 69				
					FA 69				
					FA 70				
					FA 70				
					FA 73				
					FA 73				
					FA 75				
					FA 75				
					FA 76				

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 9, 1997 (17:26)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL2 LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	76				
				FA	79				
				FA	79				
				FA	80				
				FA	80				
				FA	81				
				FA	81				
				FA	82				
				FA	82				
				FA	84				
				FA	84				
				FA	87				
				FA	87				
				FA	89				
				FA	89				
				FA	90				
				FA	90				
				FA	91				
				FA	91				
				FA	93				
				FA	93				
				FA	94				
				FA	94				
				FA	96				
				FA	96				

Tumor rate: <1% in CTL - Total

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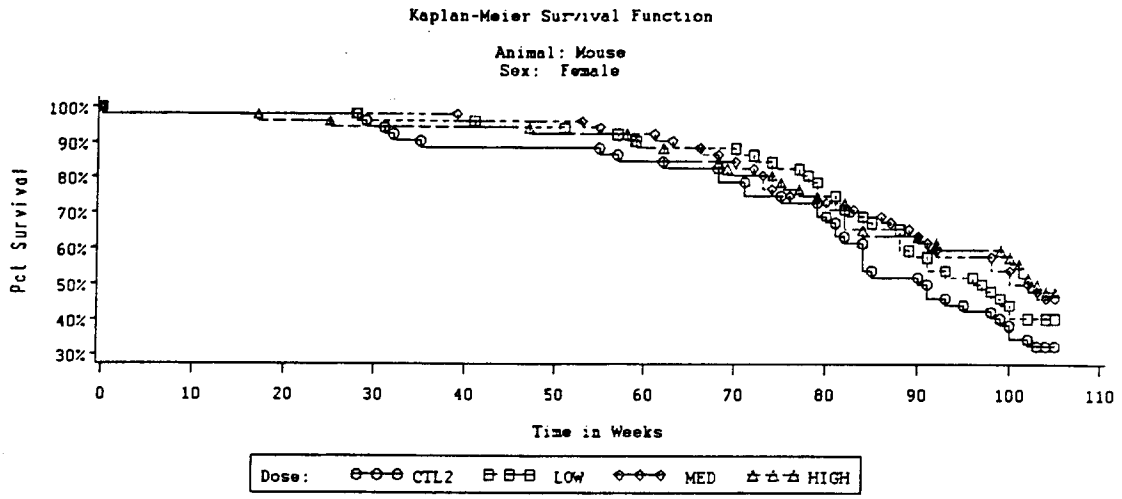
Carcinogenicity Study



Data Source: c:\b\XMICE3.TXT

Graph saved at c:\b\KM_Mou_F.sc2

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 9, 1997 (17:34)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL2 LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
**ORGANS H	(OHMS)	**HEMANGIOMA	(HMGS)	MX	IN 79-91		0.593	0.594	0.601
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 82				
					FA 82				
					FA 95				
					FA 95				
					FA 102				
					FA 102				
					FA 104				
					FA 104				
		Tumor rate: <1%		in CTL -	Total				
*OTHER ORG	(OTH)	*OTHER TUMORS	(OTH)	MX	IN 0-52		0.276	0.275	0.277
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-91				
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 28				
					FA 28				
					FA 29				
					FA 29				
					FA 31				
					FA 31				
					FA 32				
					FA 32				
					FA 41				
					FA 41				
					FA 53				
					FA 53				
					FA 55				
					FA 55				
					FA 57				
					FA 57				
					FA 59				
					FA 59				
					FA 68				
					FA 68				
					FA 69				
					FA 69				
					FA 72				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 9, 1997 (17:34)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL2 LOW MED HIGH (0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	72					
				FA	74					
				FA	74					
				FA	75					
				FA	75					
				FA	76					
				FA	76					
				FA	77					
				FA	77					
				FA	78					
				FA	78					
				FA	79					
				FA	79					
				FA	80					
				FA	80					
				FA	81					
				FA	81					
				FA	82					
				FA	82					
				FA	83					
				FA	83					
				FA	84					
				FA	84					
				FA	85					
				FA	85					
				FA	88					
				FA	88					
				FA	89					
				FA	89					
				FA	90					
				FA	90					
				FA	92					
				FA	92					
				FA	93					
				FA	93					
				FA	99					
				FA	99					
				FA	100					
				FA	100					
				FA	102					
				FA	102					

Tumor rate: <1% in CTL - Total

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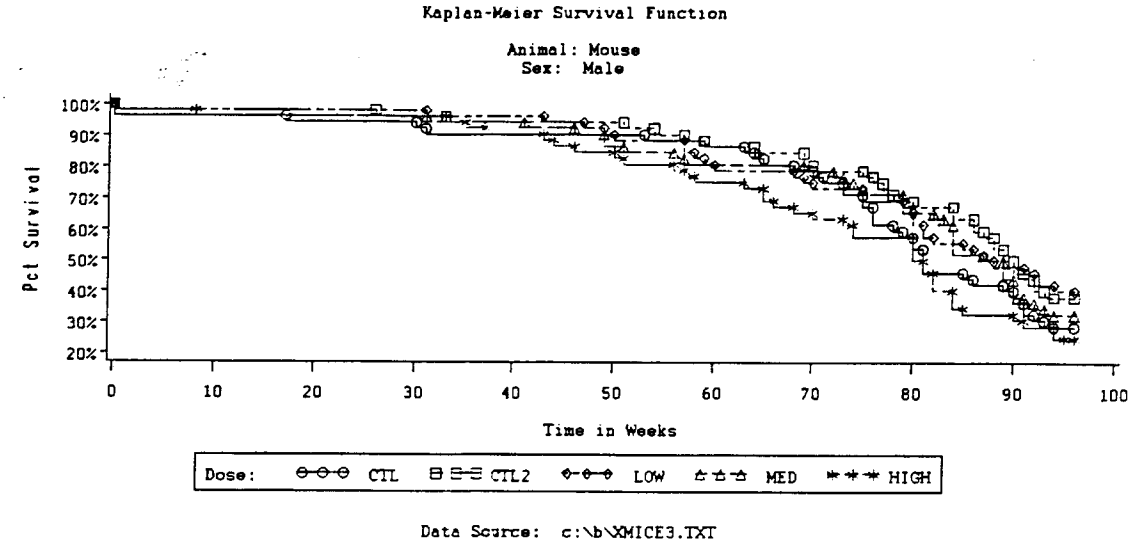
Carcinogenicity Study



Data Source: c:\b\XMICE3.TXT

Graph saved at c:\b\KM_Mou_M.sc2

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (17:00)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
**ORGANS H(OHMS		)**HEMANGIOMA (HMGS		) MX	IN 53-78		0.529	0.530	0.538
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 68				
					FA 68				
					FA 70				
					FA 70				
					FA 87				
					FA 87				
		Tumor rate: 6%		in CTL -	Total				
*OTHER ORG(OTH		)*OTHER TUMORS(OTH		) MX	IN 0-52		0.710	0.710	0.713
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-95				
					IN 79-95				
					IN 96-96				
					IN 96-96				
					FA 43				
					FA 43				
					FA 44				
					FA 44				
					FA 46				
					FA 46				
					FA 50				
					FA 50				
					FA 56				
					FA 56				
					FA 57				
					FA 57				
					FA 58				
					FA 58				
					FA 59				
					FA 59				
					FA 60				
					FA 60				
					FA 63				
					FA 63				
					FA 66				
					FA 66				
					FA 68				
					FA 68				
					FA 69				
					FA 69				
					FA 70				

(Continued)

Analysis of Carcinogenic Potential in Male Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (17:00)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

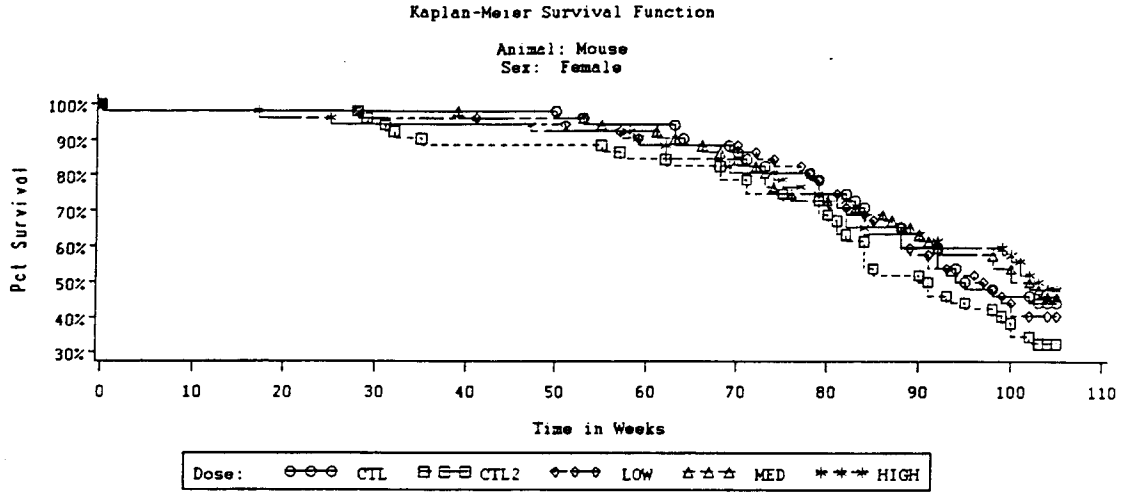
Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [`---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP- TOTIC	CONTINU CORRECT
				FA	70				
				FA	73				
				FA	73				
				FA	75				
				FA	75				
				FA	76				
				FA	76				
				FA	79				
				FA	79				
				FA	80				
				FA	80				
				FA	81				
				FA	81				
				FA	82				
				FA	82				
				FA	84				
				FA	84				
				FA	85				
				FA	85				
				FA	86				
				FA	86				
				FA	87				
				FA	87				
				FA	89				
				FA	89				
				FA	90				
				FA	90				
				FA	91				
				FA	91				
				FA	92				
				FA	92				
				FA	93				
				FA	93				
				FA	94				
				FA	94				
				FA	96				
				FA	96				

Tumor rate: 71% in CTL - Total

Page - 2 - (End of File)

Carcinogenicity Study



Data Source: c:\b\XMICE3.TXT

Graph saved at c:\b\KM_Mou_F.sc2

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Ted Guo, PH.D, CDER/FDA
Run Date & Time: February 8, 1997 (17:15)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
**ORGANS	H(OHMS	)**HEMANGIOMA	(HMGS	) MX	IN 79-91		0.391	0.398	0.405
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 82				
					FA 82				
					FA 95				
					FA 95				
					FA 102				
					FA 102				
					FA 104				
					FA 104				
		Tumor rate: 2%		in CTL -	Total				
*OTHER ORG	(OTH	)*OTHER TUMORS	(OTH	) MX	IN 0-52		0.360	0.360	0.362
					IN 0-52				
					IN 53-78				
					IN 53-78				
					IN 79-91				
					IN 79-91				
					IN 92-103				
					IN 92-103				
					IN 104-105				
					IN 104-105				
					FA 28				
					FA 28				
					FA 29				
					FA 29				
					FA 31				
					FA 31				
					FA 32				
					FA 32				
					FA 41				
					FA 41				
					FA 50				
					FA 50				
					FA 53				
					FA 53				
					FA 55				
					FA 55				
					FA 57				
					FA 57				
					FA 59				
					FA 59				
					FA 63				
					FA 63				
					FA 64				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (17:15)
Source: c: b\XMICE3.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)
Symbols [^---] [-%--] [--+-] [---*] ^ % + *
Represent 0<P<0.005 0.005<=P<0.01 0.01<=P<0.025 0.025<=P<0.05 P<.005 P<.01 P<.025 P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	64				
				FA	68				
				FA	68				
				FA	69				
				FA	69				
				FA	71				
				FA	71				
				FA	72				
				FA	72				
				FA	74				
				FA	74				
				FA	75				
				FA	75				
				FA	76				
				FA	76				
				FA	77				
				FA	77				
				FA	78				
				FA	78				
				FA	79				
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				FA	88				
				FA	89				
				FA	89				
				FA	90				
				FA	90				
				FA	92				
				FA	92				
				FA	93				
				FA	93				
				FA	98				
				FA	98				
				FA	99				
				FA	99				
				FA	100				
				FA	100				

(Continued)

Analysis of Carcinogenic Potential in Female Mouse
Test of Dose-Response (Tumor) Positive Linear Trend
Run Date & Time: February 8, 1997 (17:15)
Source: c:\b\XMICE3.TXT
Dose Levels Included: CTL CTL2 LOW MED HIGH (0 0 1.25 5 20)

Note: For TUMOR-CAUSE-DEATH not reported, assume that tumor did not cause death
Tumor Type: IN: Incidental (nonfatal) to all, FA: Fatal to all, MX: Mixed (Fatal to some)

Symbols	[^---]	[-%--]	[--+-]	[---*]	^	%	+	*
Represent	0<P<0.005	0.005<=P<0.01	0.01<=P<0.025	0.025<=P<0.05	P<.005	P<.01	P<.025	P<.05

ORGAN NAME	ORGAN CODE	TUMOR NAME	TUMOR CODE	TUMOR TYPE	TIME INTERVAL	ROW	TABLE	P VALUES EXACT PERMU	ASYMP-TOTIC	CONTINU CORRECT
				FA	102	1	0 0 0 2 0			
				FA	102	2	25 20 23 26 29			
		Tumor rate: 75%	in CTL	-	Total	-	39 35 33 33 38			

Page - 3 - (End of File)

CAC Recommendations:

1. The endpoint for both the rat and mouse carcinogenicity studies should be called a pharmacodynamic/toxicologic endpoint rather than the MTD. Requires no answer,

2. With regard to the finding of increased interstitial cell tumors in the rat study, the Committee recommended that Pharmacology consult with the sponsor regarding historical controls at the time of study and if they were in line with the positive finding in the rat carcinogenicity study the Division could make a decision whether or not to include them in the labeling. In addition the finding in male rats of an increase in pituitary cell staining for LH and FSH, considered by the sponsor to represent an increase in LH and FSH, should be

3. included in the Pharmacology Review. already in Orig Review p. 42 Results.

4. For the mouse study, the committtee recommended that Pharmacology ask Biostatistics to evaluate hemangiomas and hemangiosarcomas both separately and together as a group from all tissues. Animals with multiple tumors should be considered as one tumor finding.

4/2/97

Joseph DeGeorge, Ph.D.
Chair, CAC

cc: NDA 20-632 file
Division (HFD-510) file
HFD-510/RSteigerwalt/DHertig
HFD-510/CSO/MHess
CAC file

APPEARS THIS WAY
ON ORIGINAL

29 May 97

NDA 20-632 (Hertig; HFD-510)
MERIDIA (Sibutramine)
Knoll Pharmaceutical Company

ADDENDUM to Executive CAC minutes dtd 23 Jan 97: from David Hertig.

Follow-up to Questions posed by the Executive CAC 21 Jan 97:

1) An increased incidence of interstitial cell tumors was found in the rat carcinogenicity study.

♦According to the sponsor (Report TX92034), this finding was significantly higher than in either of the concurrent control groups (individually or combined), and was above the background incidence in the laboratory. They report that it was however, within the background range of another laboratory using Sprague-Dawley rats from the same source.

♦The sponsor has included this finding in the labeling.

2) There was an increase in pituitary cell staining for LH and FSH in male rats, which was considered by the sponsor to represent an increase in LH and FSH.

♦This finding was included in the Pharmacology Review of the NDA. / p. 42
Original

3) Two cases of benign hemangioma were found in the uteri of two high dose mice. Pharmacology requested Biostatistics to evaluate hemangiomas and hemangiosarcomas separately and together as a group for the mouse study [Consult dtd. 10 Feb 97].

♦All p-values were non-significant.

In addition the sponsor also supplied further comments and reprints regarding hemangiomas in the uterus of mice with the conclusion that hemangioma are relatively common tumors in different strains of mice, and are frequently found in the uterus.

♦It will not be necessary to include the hemangioma findings in the labeling.

ORIGINAL

Date: 23 Jan 97
From: David Hertig
Subject Exec CAC - NDA 20-632 (Draft)
To: Joseph DeGeorge
To: Joseph F. Contrera (HFD-900)
To: Joe Sun (HFD-570)
CC: Glenna Fitzgerald (HFD-120)
CC: Ronald Steigerwalt (HFD-510)

Executive CAC
21 Jan 97

Committee members:
Joseph DeGeorge, Ph.D., Chair (HFD-24)
Joseph F. Contrera. Ph.D. (HFD-900)
Joe Sun, Ph.D., Rotating Member (HFD-570)

NDA 20-632 (Hertig; HFD-510)
MERIDIA (Sibutramine)
Knoll Pharmaceutical Company

Rat Carcinogenicity Study;
The sponsor submitted study results from a completed 2-year carcinogenicity study in rats using doses of 0, 0, 1, 3, 9 mg/kg daily in the diet. The sponsor based the dose selection on MTD. The dose was adequate as determined by changes consistent with CNS stimulation and bodyweight loss (average bodyweights low through high dose were lower than controls by 3, 9, and 12% for males and 4, 10 and 13% for females). The overall incidence of benign and malignant tumors was reported not to be affected by sibutramine. There was a significant negative trend in the incidence of mammary fibroadenomas in treated males (p=0.02) and treated females (p=0.04 - within range of controls). There was an increase in the incidence of benign interstitial-cell (Leydig cell) tumors (1, 5, 6, 6, control - high dose) of the testes (significant positive trend: p=0.013). The incidence of interstitial-cell hyperplasia was higher in mid-dose (but not high dose) males. Investigations in male rats showed an increase in intensity in pituitary cell staining for LH and FSH of sibutramine treated rats which the sponsor concluded would result in an increase in LH and FSH. Plasma levels were not measured. The Division concurred with the sponsor that the interstitial cell tumors are probably hormonally mediated species specific (did not appear in mice) tumors not relevant for man.

Mouse Carcinogenicity Study:
The sponsor also submitted study results from a completed carcinogenicity study in mice using doses of 0, 0, 1.25, 5, 20 mg/kg daily in the diet. The dose was adequate as determined by changes consistent with CNS stimulation and bodyweight loss (compared to controls mean values were lower by 6 to 9% for males and 4 to 7% for females). The overall incidence of benign and malignant tumors was not affected and there were no statistically significant increases in any individual type of tumors. However, hemangioma (benign) seen in the uterus of two high dose females showed a positive trend (p=0.0027).

CAC Recommendations:
The endpoint for both the rat and mouse carcinogenicity studies should be called a pharmacodynamic/toxicologic endpoint rather than the MTD.

With regard to the finding of increased interstitial cell tumors in the rat study, the Committee recommended that Pharmacology consult with the sponsor regarding historical controls at the time of study and if they were in line with the positive finding in the rat carcinogenicity study the Division could make a decision whether or not to include them in the labeling. In addition the finding in male rats of an increase in pituitary cell staining for LH and FSH, considered by the sponsor to represent an increase in LH and FSH, should be included in the Pharmacology Review.

For the mouse study, the committtee recommended that Pharmacology ask Biostatistics to evaluate hemangiomas and hemangiosarcomas both separately and together as a group from all tissues. Animals with multiple tumors should be considered as one tumor finding.

4/2/97

Joseph DeGeorge, Ph.D.
Chair, CAC

cc: NDA 20-632 file
Division (HFD-510) file
HFD-510/RSteigerwalt/DHertig
HFD-510/CSO/MHess
CAC file

APPEARS THIS WAY
ON ORIGINAL