NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS' MEETING
January 8, 1986

Peer Review of the Data from the Chronic Carcinogenesis
Animal Bioassay of FD and C Yellow No. 6 By
The Technical Reports Review Subcommittee and Panel of Experts

Summary Minutes

The National Toxicology Program (NTP) Board of Scientific Counselors Technical Reports Review Subcommittee and ad hoc Panel of Experts (the Panel) met at 1:00 p.m. on January 8, 1986, in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. This open meeting was held at the request of the Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA), for the purpose of providing independent peer review of the data from the chronic carcinogenesis bioassay of FD and C Yellow No. 6 (Yellow 6) in Charles River Sprague-Dawley rats. The bioassay was sponsored by the Certified Color Manufacturers Association, conducted by Bio/dynamics, Inc., and submitted to the FDA in support of permanent listing of FD and C Yellow No. 6 (Attachment 1: Federal Register Meeting Announcement; Attachment 2: Agenda). In advance of the meeting, the peer reviewers were provided by the CFSAN with a data package consisting of: the charge from the Director, CFSAN; an executive summary; memoranda from the Divisions of Toxicology, Pathology and Mathematics; information on the genetic toxicology and chemistry of the color; a review by the Center's Cancer Assessment Committee; and supporting statistical and pathology tables. Also prior to the meeting, the four pathologists associated with the Panel examined slides of kidney sections from male and female rats on the study. Dr. James Swenberg, member of the Subcommittee, chaired the meeting. Peer reviewers are listed in Attachment 2.

Dr. W. G. Flamm, FDA, stated the charge to the Panel as initially expressed in a letter from Dr. Sanford Miller, Director, CFSAN, to Dr. David P. Rall, Director, NTP. As follows: "the issue requiring peer review revolves around the occurrence of a higher number of proliferative renal lesions in female rats that were treated at the highest dose of FD and C Yellow No. 6 as compared to control rats; does this observation show that Yellow 6 is a carcinogen? If not, is the nature of the data such that it would or would not preclude FDA from making a finding that the color additive is safe within the meaning of the Food, Drug and Cosmetic Act? Allied to this question were two others which FDA wanted examined: (1) What is the role of chronic progressive nephrosis in the pathogenesis of renal proliferative lesions in rats fed diets with the high dose of Yellow 6?, and (2) Does the occurrence of a greater number of proliferative renal lesions (even without additional sectioning) in untreated male control rats influence the interpretation of a possible relationship to exposure to the chemical." Dr. Flamm concluded by asking that the Panel be as definitive in their scientific judgment as the weight of evidence would allow. In response to

Dr. Swenberg, he asked that the Panel consider all of the experimental evidence and not just that from the female rat in arriving at their conclusions.

Toxicology Review: Dr. Benjamin Jackson, CFSAN, presented an overview of the toxicology of Yellow 6 which chemically is the disodium salt of 6-hydroxy-5-((4-sulfophenyl)azo)-2-naphthalene sulfonic acid. Included wererr summaries of toxicity results from acute, subchronic and chronic oral dosingrr studies in mice, rats, pigs and dogs. Toxicity, expressed as decreasedrr weight gain, diarrhea or bone marrow hyperplasia, was observed only at highrr dose levels in rodents and dogs. No adverse effects were reported in the three-generation reproduction studies in rats and conventional teratology studies inrr rats and rabbits. With the single exception of a positive result reported inrr the literature for chromosome aberrations in an in vitro test, the various typesrr of genetic toxicology studies reported by others or done in FDA laboratoriesrr with Yellow 6 have had negative results. In previous long-term studies in micerr and dogs, no carcinogenic effects were reported. This was also the case in sixrr previous chronic feed studies in rats at doses ranging from 0.03 to 5%.rr Although there was one study with findings suggestive of an increase in mammaryrr tumors at two dose levels, the observation was not repeated in the same laboratory with exposure of large numbers of animals.rr

Pathology Review: Dr. Ronald Moch, CFSAN, discussed the findings in the kidneys of control and dosed male and female rats from both studies performed by Biodynamics, Inc., for the CCMA, the first study (No. 77-1778) having two control groups and three dose groups (0.75%, 1.5%, and 3.0% in the diet) while the second study (No. 78-2211) had one control and one dose group, 5.0%. The issue of most concern had to do with an increased incidence as diagnosed by the contractor pathologists of renal cortical adenomas (4/70) and a renal cortical carcinoma (1/70) in female rats receiving 5.0% of Yellow 6 in the diet as compared with none in concurrent controls. The CFSAN pathologists observed renal cortical adenomas in 5/70 of the female rats and questioned the diagnosis of renal cortical carcinoma in one of the rats. In an attempt to further define these observations, the decision was made to recut 10 additional sections per kidney. This resulted in a marked increase in the number of rats with renal cortical adenomas as diagnosed by the contractor pathologists in the female rats receiving 5% Yellow 6 in the diet (16/70) with 4/70 reported in controls. The pathologists in CFSAN reported no change in the incidence of rats with renal cortical adenoma but did diagnose nodular hyperplasia in rats in both control (9/70) and the 5.0% dose group (12/70). After the additional sectioning of kidneys, none of the pathologists considered any of the renal cortical proliferative lesions to be renal cortical carcinomas. Nearly all rats diagnosed with proliferative lesions were diagnosed as also demonstrating chronic progressive nephrosis. Dr. Moch then reviewed the findings for male rats from both studies. In male rats the most notable results were seen in the first study where the contractor pathologists reported higher incidences of proliferative renal lesions in control animals than in animals dosed with Yellow 6.

Dr. Moch stated that no universally accepted morphologic criteria exist for differentiating a hyperplastic lesion from a benign neoplastic lesion of the rat kidney. In part, this could explain differing diagnoses among pathologists from Bio/dynamics, Inc., CFSAN, and Experimental Pathology Laboratories

one factor complicating the interpretation of the study as related to chemical treatment was the presence of chronic progressive nephrosis. He said that whether the renal proliferative lesions arose from, were exacerbated by, or were merely concurrent with chronic progressive nephrosis was not readily apparent. Further, the proliferative lesions in treated female rats were, in general, small microscopic foci. Except for one rat with a tubular adenomal in the 1.5% group, none of the control or treated female rats in the first (lowerdose) studies (No. 77-1778) were diagnosed as having proliferative lesions. In male rats, nodular hyperplasias were observed in both the control group and treated group from the second study, and based on CFSAN pathologist's evaluations, no renal cortical adenomas or carcinomas were observed in either control or treated rats, while in the first study, malignant neoplasms in kidneys were reported only in control animals. Based on CFSAN and Biodynamics' pathologists' evaluations, no malignant tubular cell neoplasms of the renal cortex were identified in treated rats of either sex in either study. Finally, he stated that historically, chemically-induced renal proliferative lesions have been observed more frequently in male than in female rats.

Observations Supporting or Not Supporting A Carcinogenic Effect of FD and C Yellow No. 6: Dr. Jackson said there were two observations that suggested a carcinogenic effect: (1) the higher number of female rats with proliferative renal cortical lesions in the group fed 5% Yellow 6 than in controls; and (2) the reported apparent rarity of proliferative renal cortical lesions in historical control animals following routine sampling.

He summarized the findings and reports by others that do not lend support to there being a carcinogenic effect of Yellow 6: High Dose (5%) Females - (1) small number of affected rats with marginal statistical significance (P=0.03 for adenomas and P=0.05 for hyperplasias and adenomas combined); (2) small size (microscopically) of most lesions; (3) lack of relationship between duration of treatment and numbers of rats with lesions as well as numbers and size of lesions; (4) no evidence of progression nor observation of the full spectrum of neoplastic changes; (5) morphologic similarity between proliferative renal lesions in treated and controls; and (6) no apparent earlier occurrence of proliferative lesions in treated rats - High Dose (5%) Males - (1) no treatment related effects; (2) high incidence of male controls with lesions; and (3) morphological similarity between proliferative lesions in treated and control animals - All Other Doses, Males and Females - (1) there were no treatment related effects at lower dosages - Other Rat Strains and Other Species - (1) there were no neoplastic changes in other rat strains, in dogs, or in mice, and (2) there was no evidence that the kidney is a target organ for Yellow 6 - Other Information - (1) there is no evidence of teratogenic or other reproductive effects; (2) there were no clear positive findings in short-term tests (primarily genetic toxicology); (3) female rats previously were not known to be uniquely responsive to renal carcinogens; (4) historical control information available is based primarily on limited samplings of kidneys, i.e., one section per kidney; and (5) a reexamination of the kidney slides from the published NTP study showed no effects on the kidneys.

General Discussion by the Peer Review Panel: Dr. Kociba asked whether the diets for both control and treated rats were analyzed periodically for

Yellow 6 to assure absence of cross contamination in view of the levels of proliferative lesions in some control groups. Dr. Geoffrey Hogan, Bio/dynamics, said this was done and Yellow 6 could not be detected in control diets. Dr. Scala expressed discomfort with the additional sectioning of kidneys from female rats in the second study because he was concerned with possible selection bias and lack of randomness. Dr. Moch and Dr. Hogan described in detail the protocol used.

Discussion by the Panel of the Pathologic Findings: Dr. Kociba chaired the slide review by Drs. Bruner, Casey, Swenberg and himself and led the discussion of their interpretation of the histopathology for the control and treated female rats from the second study (No. 78-2211). The diagnostic categories used were those developed by Alden and Kinerva, Food Chemical Toxicology, 20, pp. 441-450, 1982, and encompassed to a large degree the terminology used by the study pathologists. Slides from 10 control and 19 treated rats were examined. The diagnoses made by the Panel pathologists for the control animals are shown in the table in Attachment 3 and for the treated (5% in the diet) animals in Attachment 4. Dr. Kociba commented that:

(1) the kidneys from both control and treated groups showed an advanced degree of chronic progressive nephropathy;

(2) there was unanimity that there were no carcinomas of renal tubular origin in any of the rats;

(3) the only malignancies were transitional cell carcinomas (one control, one treated) and an undifferentiated malignant neoplasm (treated);

(4) there was considerable divergence of opinion as to diagnoses among the various categories of renal tubular hyperplasias and adenomas;

(5) there was the appearance that a higher percentage of the treated animals had some type of proliferative lesion, hyperplasia or adenoma, than did the controls. This was based on the best representation being cases where at least two of the four pathologists concurred; for this study there would be seven treated vs two control animals with renal tubular adenomas;

(6) after limited examination of slides from control male rats there was concurrence with the reported higher incidence than in treated rats of renal tubular proliferative lesions.

Dr. Kociba concluded by stating that whether or not treatment with Yellow 6 exacerbated the chronic nephropathy observed or any chronic changes related to the nephropathy, e.g., hyperplasia, could not be determined from the available data.

In other discussion, Dr. Swenberg said the pathologists were surprised by the large numbers of proliferative lesions in female rat kidneys albeit these were life-time studies. He noted that in female rats there was only one grossly visible lesion in a treated animal while there were several grossly visible in male control animals.

General Discussion by the Panel: There was some discussion about the variable historical incidences of renal tumors (based on one section per kidney) in male or female control rats from life-time studies with various other colors. It was agreed that the NTP Levels of Evidence for Carcinogenicity would not be applied formally to the data on Yellow 6 although they could be used for purposes of discussion. Rather, a conclusion(s) could be formulated reflecting a consensus of the Panel. With this in mind, Dr. Scala opined that the data for female rats in the second study might be at best equivocal for carcinogenicity while the overall conclusion for the color would be no evidence of carcinogenicity. Dr. Swenberg noted that the data in the tables (Attachments 3 and 4) represented worst case diagnoses so many of the animals also may have had lesser lesions. Dr. Bruner, pathology consultant to the Panel, observed that based on the male rats there were not dose-related effects but certainly in the females a possible relation between nephropathy and increased numbers of proliferative lesions might exist. Dr. Flamm commented that the Sprague-Dawley rat was not a good model for trying to assess nephrotoxicity. Dr. Casey, pathology consultant to the Panel, said that considering these were life-time studies the lack of progression of lesions from benign to malignant status supported a view that Yellow 6 was not a carcinogen.

Conclusions Approved by the Peer Review Panel: Dr. Kociba formulated a draft statement in response to the charge to the Panel by the FDA, and two statements in response to the two allied questions. The primary statement was supported by five points. During discussion, the reviewers generally agreed with the statement with minor or clarifying modifications and inclusion of three additional supporting points. Since this statement centered on the data in female rats from the second study, the Panel drafted a supplementary conclusion which addressed the overall weight of evidence regarding the carcinogenicity of Yellow 6, i.e., taking into consideration previous studies with Yellow 6 discussed during the meeting. The statements in response to the allied questions were affirmed without debate. The primary conclusion with supporting points, the supplementary conclusion on the totality of evidence, and the responses to the two allied questions were approved unanimously by the Panel. They are as follows:

Primary Conclusion: Evaluation of pertinent study data and selected slides of kidney lesions from female Sprague-Dawley rats used in a long-term study of 5% FD and C Yellow No. 6 in the diet (Biodynamics Study #78-2211) indicated that the resultant study data were considered insufficient to be categorized as a demonstrated carcinogenic response to the chemical treatment.

This interpretation is based on consideration of:

(1) the acknowledged debatable nature of the small renal proliferative lesions variously categorized by different pathologists as representing nodular hyperplasia, adenomatous hyperplasia or benign renal tubular adenomas;

(2) the lack of concurrence as to whether lesions were hyperplastic or benign neoplastic, noted upon inspection of the incidence

rates reported for these lesions by different examining pathologists, i.e., those from Bio/dynamics, Division of Pathology (CFSAN), Experimental Pathology Laboratories, and the Peer Review Panel;

(3) with one exception, the unanimous agreement among the different examining pathologists of the absence of any definitive malignant renal cortical tubular neoplasms in the treated rats;

(4) the relatively unique condition wherein up to 20 sections (10 per kidney) were examined from each of the control and treated female rats from the high dose (5%) study;

(5) the absence of any type of renal tubular proliferative response in the male rats (generally regarded as more sensitive than female rats to experimental renal tubular neoplasias) used in this study;

(6) the negative genetic toxicology data base;

(7) the previously reported chronic studies which were all negative for carcinogenicity; and

(8) the judgment that the dose chosen was a good approximation of the maximum tolerated dose (MTD).

Supplemental Conclusion: In evaluating Study No. 78-2211 along with all others, the weight of evidence of all the studies does not suggest that FD and C Yellow No. 6 is a renal carcinogen.

Response to the First Allied Question: The data available do not allow a definitive judgment to be made regarding what role the chronic progressive nephrosis may have played in the formation of the renal tubular proliferative lesions observed in both control and treated female rats used in the study.

Response to the Second Allied Question: The occurrence of renal cell carcinomas in two untreated control groups of male rats of a companion study (with zero incidence rates in the treated groups of male rats) was considered to be a supportive factor in the overall weight of evidence interpretation of the data from the female rats used in Study No. 78-2211.

contribute to the committee's work. This would involve, for example, an understanding of research design, benefit/risk, and the legal requirements for safety and efficacy of the products under review, and considerations regarding individual products. The agency notes, however, that for some advisory committees, it may require such nominees to meet the same technical qualifications and specialized training required of other expert members of the committee. The term of office for these members is 4 years. Nominations for all committees listed above are invited for consideration for membership as openings become available.

Nomination Procedure

Any interested person may nominate one or more qualified persons for membership on one or more of the advisory committees. Nominations shall specify the committee for which the nominee is recommended. Nominations shall state that the nominee is aware of the nominations, is willing to serve as a member of the advisory committee, and appears to have no conflict of interest that would preclude committee membership. Potential candidates will be asked by FDA to provide detailed information concerning such matters as financial holdings, consultancies, and research grants or contracts in order to permit evaluation of possible sources of conflict of interest.

This notice is issued under the Federal Advisory Committee Act (Pub. L. 92–463, 86 Stat. 770–776 (5 U.S.C. App. I) and 21 CFR Part 14, relating to advisory committees.

Dated: December 9, 1985.

Mervin H. Shumate,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 85–29772 Filed 12–16–85; 8:45 am]

BILLING CODE 4160–01–M

Public Health Service

National Toxicology Program Board of Scientific Counselors Meeting

Pursuant to Pub. L. 92–463, notice is hereby given of the meeting of the National Toxicology Program Board of Scientific Counselors, U.S. Public Health Service, in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, on January 8, 1986.

The meeting will be open to the public from 1:00 p.m. until adjournment for the purpose of providing peer review of the data from the chronic carcinogenesis bioassay of FD and C Yellow No. 6 in male and female Charles River albino rats. The bioassay was sponsored by the Certified Colors Manufacturers Association, conducted by Biodynamics, Inc., and submitted to the Food and Drug Administration (FDA) in support of permanent listing of FD and C Yellow No. 6 for food, drug and cosmetic uses. The review will be performed by the Technical Reports Review Subcommittee of the Board in conjunction with an *ad hoc* panel of experts.

The meeting will commence with a brief overview of the studies. This will be followed with presentations by scientific staff from the Center for Food Safety and Applied Nutrition, FDA, concerning the pathology findings. Sufficient time will be allowed for public comment.

The Executive Secretary, Dr. Larry G. Hart, Office of the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709, telephone (919) 541–3971, FTS 629–3971, will furnish program information prior to the meeting and summary minutes subsequent to the meeting.

Dated: December 10, 1985.

David P. Rall, M.D., Ph.D.

Director, National Toxicology Program.

[FR Doc. 85–29765 Filed 12–16–85; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF THE INTERIOR

Central and Field Organization

This notice provides a description of the central and field organization of the Department of the Interior, including the functions of the bureaus and offices and places at which the public may obtain information.

This notice is published in accordance with the provisions of 5 U.S.C. 552(a)(1)(A) and supersedes the notice published in the **Federal Register** on May 26, 1979 (44 FR 30451). Additional information regarding the Department's functions and programs may be obtained by directly contacting the appropriate bureau or office and referring to the public regulations of the Department as published in Titles 25, 30, 36, 41, 43, 48, and 50 of the Code of Federal Regulations.

Dated: December 6, 1985.

Joseph E. Doddridge, Jr.,

Deputy Assistant Secretary of the Interior.

Office of the Secretary

Secretary

The Secretary of the Interior, as the head of an executive department, reports directly to the President and is responsible for the direction and supervision of all operations and activities of the Department. The Secretary also has certain powers or supervisory responsibilities relating to Territorial governments.

Under Secretary

The Under Secretary assists the Secretary in the discharge of Secretarial duties and serves as Acting Secretary in the asbsence of the Secretary. With the exception of certain matters reserved by the Secretary, the Under Secretary has the full authority of the Secretary.

Fish and Wildlife and Parks

The Assistant Secretary for Fish and Wildlife and Parks discharges the duties of the Secretary with the authority and direct responsibility for programs associated with the development, conservation, and utilization of fish, wildlife, recreation, historical, and national park system resources of the Nation. The Assistant Secretary represents the Department in the coordination of marine environmental quality and biological resources programs with other Federal agencies. The Assistant Secretary for Fish and Wildlife and Parks exercises Secretarial direction and supervision over the United States Fish and Wildlife Service and the National Park Service.

Water and Science

The Assistant Secretary—Water and Science discharges the duties of the Secretary with the authority and direct responsibility to carry out the statutory mandate to manage and direct programs supporting the development and implementation of national water and minerals policies through encouraging and assisting the development of economically and environmentally sound resource activities, including development and conservation of hte Nation's water supply and support of cost-sharing techniques for development and management of water supplies in the 17 Western States; water resource evaluation and analysis; fostering and encouraging the private sector in the orderly and economic development of domestic mineral resources; effective mineral data collection and analysis; assessment of frontier area mineral resources for long-term availability; improved focus and effectiveness of departmental research and development activities in geology, hydrology,

AGENDA

Board of Scientific Counselors
National Toxicology Program

January 8, 1986
1:00 p.m.

Conference Center, Building 101
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

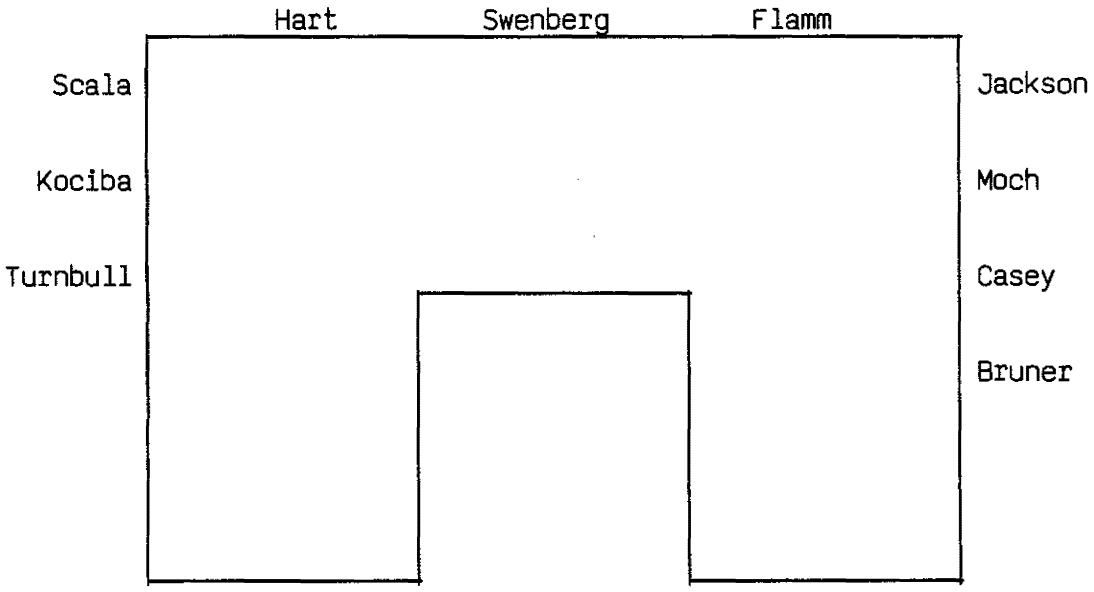
Peer Review of the Data from the Chronic
Carcinogenesis Animal Bioassay of FD and C Yellow No. 6
By the Technical Reports Review Subcommittee and Panel of Experts

Overview	Dr. W. G. Flamm, Director, Office of Toxicological Sciences, Center for Food Safety and Applied Nutrition, FDA
Discussion of Toxicology	Dr. B. A. Jackson, Director, Division of Pathology, Center for Food Safety and Applied Nutrition, FDA
Discussion of Pathology	Dr. R. W. Moch, Assistant for Pathology Coordination, Office of Toxicological Sciences, Center for Food Safety and Applied Nutrition, FDA
Public Comments	
Peer Reviewer Comments and Discussion of Data from Bioassay of FD and C Yellow No. 6	Peer Review Panel
Conclusions	Peer Review Panel

NTP PEER REVIEW OF THE DATA ON FD AND C YELLOW NO. 6

Conference Center, Building 101
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

January 8, 1986



National Toxicology Program
Board of Scientific Counselors
Technical Reports Review Subcommittee and Panel of Experts

January 8, 1986

Subcommittee Member

Dr. James Swenberg (Chairman)
Head, Department of Biochemical
Toxicology and Pathobiology
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Panel Members

Dr. Richard J. Kociba
Dow Chemical USA
Midland, MI

Dr. Robert A. Scala
Senior Scientific Advisor, Medicine
and Environmental Health Department
Research and Environmental Health
Division
Exxon Corporation
East Millstone, New Jersey

Panel Members (Cont'd)

Dr. Bruce W. Turnbull
Professor and Associate Director
College of Engineering
Cornell University
Ithaca, New York

Expert Pathology Consultants

Dr. Richard H. Bruner
Toxicology Detachment
Naval Medical Research Institute
Wright-Patterson AFB, Ohio

Dr. Harold W. Casey
Department of Veterinary Pathology
School of Veterinary Medicine
Louisiana State University
Baton Rouge, LA

TABLE 1

Results of the Pathology Review of Kidney Slides from
Control Female Rats - Study No. 78-2211 by the
NTP Peer Review Panel Pathologists on January 7-8, 1986[a,b]

Case No.	No. Proliferative Lesions	Simple Tubular Hyperplasia	Nodular Hyperplasia	Adenomatous Hyperplasia	Renal Tubular Adenomas	Renal Tubular Carcinomas	Other Diagnoses
1501	2/4		2/4				
1511		2/4	2/4				
1517		3/4		1/4			
1520		3/4	1/4				
1532		1/4	2/4	1/4			
1549	1/4	2/4	1/4				
1552	2/4	1/4	1/4				
1555			1/4	1/4	2/4		
1556				2/4	2/4		
1568							3/4[c] 1/4[d]
	3/10/70	6/10/70	7/10/70	4/10/70	2/10/70	0/10/70	

[a]n/4=number of Panel pathologists making a diagnosis/total number of Panel pathologists

[b]n/10/70=number of animals diagnosed/number of animals examined/total number of animals in group

[c]Diagnosed lesion as transitional cell carcinoma

[d]Diagnosed lesion as transitional cell hyperplasia

ATTACHMENT 3

TABLE 2

Results of the Pathology Review of Kidney Slides from Treated Female Rats (FD and C Yellow No. 6 - 5% in Diet) - Study No. 78-2211 - by the NTP Peer Review Pathologists on January 7-8, 1986[a,b]

Case No.	No. Proliferative Lesions	Simple Tubular Hyperplasia	Nodular Hyperplasia	Adenomatous Hyperplasia	Renal Tubular Adenomas	Renal Tubular Carcinomas	Other Diagnosis
2503			1/4	2/4	1/4		
2507					4/4		
2512				3/4	1/4		
2515	2/4		2/4				
2522	1/4	2/4	1/4				
2524			2/4	2/4			
2525					4/4		
2530			1/4	3/4			
2541		1/4	1/4	2/4			
2550				1/4	3/4		
2551					4/4		
2553				2/4	2/4		
2554							4/4[c]
2555				2/4	2/4		
2560		2/4	2/4				
2564			2/4	2/4			
2566		2/4	1/4	1/4			
2568					4/4		
2549							4/4[d]
	2/19/70	4/19/70	9/19/70	10/19/70	9/19/70	0/19/70	

[a]n/4=number of Panel pathologists making a diagnosis/total number of Panel pathologists
[b]n/19/70=number of animals diagnosed/number of animals examined/total number of animals in group
[c]Diagnosed lesion as malignant undifferentiated neoplasm, NOS
[d]Diagnosed lesion as transitional cell carcinoma

ATTACHMENT 4