8-21-91

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

August 21, 1991

FILE COPY

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Second Carcinogenicity Peer Review Meeting on **Cyproconazole**

FROM: Esther Rinde, Ph.D. E.R.
Manager, Carcinogenicity Peer Review
Health Effects Division (H7509c)

TO: Addressees

The HED Carcinogenicity Peer Review Committee (CPRC) first met to consider Cyproconazole on June 20, 1990. The (CPRC) concluded that Cyproconazole should be classified as a Group C carcinogen and that a low dose extrapolation model (Q1*) be used for quantification of potential human cancer risk.

The CPRC is now asked to re-consider the evidence, in light of the Registrant's submission which is summarized in the attached memo from Dr. Linda Taylor. A copy of the Peer Review Document for the June 20 meeting and the Qualitative Risk Assessment and Genetic Toxicity memos are also included, for your information.

A meeting to re-consider the evidence for Cyproconazole is scheduled for **Wednesday, Sept. 11, 1991, at 10:00 am in Room 821, CM2.**

Addressees

P. Fenner-Crisp
W. Burnam
R. Engler
R. Hill
R. Beliles
K. Baetcke
L. Brennecke
M. Van Gemert
M. Copley
K. Dearfield
J. Parker
E. Saito (for microfiche-with one-liner)
H. Pettigrew
W. Sette
G. Ghali
B. Fisher
J. Du
Y. Woo
G. Burin
J. Quest
L. Taylor
C. Swentzel

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WASHINGTON, D.C. 20460

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AUG 19 1991

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Cyproconazole: Peer Review of Cyproconazole; Reconsideration of (1) Mouse Liver Tumor Data; Suitability for Quantitative Risk Assessment; (2) Adequacy of Dose Levels in Rat Study

TO: Esther Rinde, Ph.D.
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 8/14/91
Toxicology Branch II, Section II
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 8/14/91
Section Head II, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 8/14/91
Chief, Toxicology Branch/HFAS/HED (H7509C)

Registrant: Sandoz Crop Protection Corporation
Chemical: α-(chlorophenyl)-α-(1-cyclopropylethyl)-1H-1,2,4-triazole-1-ethanol
Synonyms: Cyproconazole
Caswell No.: 272E

Cyproconazole was evaluated by the HED Peer Review Committee on June 20, 1990 and placed in Group "C", possible human carcinogen, based upon increased incidence of hepatocellular adenomas and carcinomas in male and female CD-1 mice. Quantification of potential human cancer risk using the low-dose extrapolation model ($Q1^*$) was also recommended.

A summary of the Registrant's submission is presented below. It is requested that the Peer Review Committee reconsider (1) the suitability of the liver tumor data (from the mouse carcinogenicity study on Cyproconazole) for quantitative risk assessment and (2) the adequacy of the high dose in the rat chronic toxicity/ carcinogenicity study.

The Registrant (Sandoz Crop Protection Corporation) has submitted

an outside scientific review group evaluation of the data (see attached TB II review of that evaluation), which they believe has generated new scientific information that is "highly significant and likely to warrant new conclusions and recommendations by the HED Peer Review Committee with respect to the purported carcinogenicity of Cyproconazole." All of the histopathology for the liver in the mouse study was reread by the Chairperson and presented for consideration to the Peer Review Panel (PRP). The following conclusions were offered:

1. Cyproconazole shows no evidence of mutagenic activity whatsoever, based on an exhaustive battery of tests, including gene mutations, structural aberrations, numerical aberrations, genetic damage, or cell transformation. Cyproconazole is therefore not mutagenic and cannot be considered an initiator in somatic carcinogenesis.

2. Cyproconazole was administered in the diet to rats in a valid lifetime carcinogenic bioassay in which there is clear evidence both that a Maximum Tolerated Dose (MTD) was achieved and that no carcinogenic effects were observed.

3. An independent pathology peer review panel found in a lifetime feeding study in mice that liver tumors were induced only in the presence of overwhelming cytotoxicity (i.e., hepatic lytic necrosis) in the high-dose animals. The panel concluded that these cytotoxic effects at high doses altered the physiological conditions of the animals to the extent that the liver tumors, which otherwise might not have occurred, were induced or promoted."

Under these circumstances, the Registrant concludes that "the relevance of the induced mouse liver tumors is not only highly questionable to predictions of human health risks, but the use of low-dose extrapolation dose-response models based on this endpoint (e.g., Q^*1) to estimate human risk is both inappropriate and not recommended." (see TB II memo regarding contractor's evaluation of the data, copy attached)

DISCUSSION

Mutagenicity: With regard to the mutagenicity issue, TB II notes that a recently submitted chromosomal aberration mutagenicity study (DER dated 6/17/91, cover memo dated 7/8/91) supports the previous (similar) study's findings, which indicate that Cyproconazole is clastogenic in this (Chinese hamster ovary cells) test system. Additionally, the Peer Review Committee identified the need to perform a dominant lethal assay in rats with Cyproconazole to help resolve the issue of potential heritable germ cell effects.

Rat Study: With regard to the issue of whether the high dose in the rat chronic toxicity/carcinogenicity study was sufficiently high to adequately assess the carcinogenic potential of Cyproconazole, the

Registrant's consultant reiterates their previous arguments (TB II memo dated 3/20/91) that the body-weight gain decrements were biologically significant, especially when the liver weight is subtracted from the body weight.

Aspects ignored include the fact that the liver effects (histological changes) were reversible in the subchronic study, there was a lack of consistent liver enzyme effects, and no life-threatening histopathological lesions. The Registrant argues that the most structurally similar compounds (propiconazole, triadimefon, and triadimenol) have not produced carcinogenic effects in rats at high (2000-5000 ppm) doses, but TB II notes that hexaconazole has produced testicular tumors in the rat at 1000 ppm. Additionally, there is nothing "magic" in the 10% figure stated in the MTD document, which in fact states should reach 10-15%. What determines whether a particular dose is adequate is the total picture; i.e., body-weight gain deficit, organ weight effects accompanied by toxic lesions, not adaptive lesions. The recovery phase of the rat subchronic study clearly showed that the liver lesions observed were adaptive measures. There was no demonstration of a spectrum of histopathological change in the liver of rats in that study. As stated in the MTD document quoted by the consultant, in the past chronic studies on various hepatotoxins were performed at doses based on organ weight increases, cloudy swelling and vacuolation, alone or in combination and the doses were not adequate, as in the case of Cyproconazole. These lesions are often not life-threatening. The lesions displayed in the Cyproconazole subchronic study were vacuolated hepatocytes and enlarged hepatocytes, which were not observed after the recovery period. Although the high dose in the long-term study was 30 ppm higher than that (320 ppm) in the subchronic study, given the minimal toxicity observed and the reversibility of the liver effects, the rats would have tolerated higher doses. The high dose in the 4-week study was 1000 ppm, which did not cause any deaths or treatment-related symptoms, although there was a significant decrease in body-weight gain at this level (and food wastage). The next highest dose in that study was 300 ppm.

In the Prodiamine Peer Review, which the Registrant contends is similar to the current situation, the 2-year rat study was considered to have reached an MTD, based on body-weight gain decrement of 14.3% (males) and 8.4% (females) at a dose of 3200 ppm. The subchronic study on Prodiamine had tested dose levels of 400, 1200 and 4000 ppm, where the high dose displayed body-weight gain decrements of 13% (males) and 10 to 15% in females. Based on this significant decrease, the high dose for the carcinogenicity study on Prodiamine was set at 3200 ppm. This situation differs from the Cyproconazole situation in that the body-weight gain decrement in the subchronic study was observed in both sexes and the high-dose chosen for the long-term study also produced a body-weight gain decrement, which, although less than a 10% decrement in females, was accompanied by a compound-related increase in the

incidence of thyroid tumors.

Mouse Study: Although there were differences in diagnoses of liver lesions between the original pathologist and the PRP, both showed that Cyproconazole is a liver toxin; only the terminology and/or severity of the lesion were different. The Registrant concluded that Cyproconazole induced hepatocellular tumors that were primarily benign in the two highest dose groups of male (100 & 200 ppm) and in the highest dose group of females. Additionally, at the two highest dose levels of both sexes, there was a statistically significant increase in the incidence of lytic necrosis of the liver. The most important observation of the outside peer review, according to the Registrant, was that the "liver cell damage was present at termination and, therefore, must have occurred throughout the lifespans of the animals. Such a degenerative process in the liver invariably results in increased regenerative cellular proliferation, and the important role of cellular proliferation in tumor development is well recognized.[2] At low, non-toxic doses, there would be no increase in cell proliferation to promote tumor development." The Registrant concluded that the induced tumors appear to be the result of promotion of spontaneously initiated cells, given the lack of genotoxicity and the occurrence of tumors only at doses that were hepatotoxic. It was further concluded that the tumor data are not suitable for quantitative risk assessment.

CONCLUSION: The issues to be addressed are: (1) whether the rat study will be accepted as adequate; (2) does the liver toxicity as presented by the Registrant alter the Committee's assessment of the carcinogenic potential of Cyproconazole; (3) is it appropriate to change a chemical's classification when all of the data are not available; i.e., additional mutagenicity study requested by the Committee/lack of an adequate rat study (if current study inadequate).

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Cyproconazole: Outside Contractor's Evaluation of Carcinogenicity Data

TO: Carl Grable
Product Manager (21)
Registration Division (H7509C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 8/1/91
Toxicology Branch II, Section II
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 8/8/91
Section Head II, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D.
Chief, Toxicology Branch/HFAS/HED (H7509C)

Registrant: Sandoz Crop Protection Corporation
Chemical: α-(chlorophenyl)-α-(1-cyclopropylethyl)-1H-1,2,4-triazole-1-ethanol
Synonyms: Cyproconazole
Project No.: 1-0962
Caswell No.: 272E
Record No.: None provided
Identifying No.: 055947-RGG
MRID No.: N/A
Action Requested: Please review outside contractor evaluation of carcinogenicity data for Cyproconazole.

Comment: In response to the conclusions reached by the HED Peer Review on Cyproconazole, the Registrant contracted with Clement International Corporation and their consultants for assistance in evaluating all of the evidence on Cyproconazole with respect to its possible carcinogenicity, reproductive, and teratogenic potential. In the current submission, only the issue of carcinogenicity is discussed. The following documents were submitted:

1) Evaluation of the Experimental Data for Cyproconazole;
2) Pathology Review Panel on the Chronic Toxicity/Oncogenicity Study of SAN 619F in CD-1 Mice;
3) Appendices A through D.

Subsequent to the submission of these data, a meeting was held at which the Registrant and consultants presented their findings. It was agreed, following the presentation, that an additional summary/discussion of the data would be provided to the Agency for review with regard to the issue of MTD. This latter information has been submitted and is included with this review.

MOUSE STUDY

Background: A pathology peer review of the liver neoplastic and nonneoplastic lesions observed in the mouse study was performed by MR Anver (Chairperson), who had access to the laboratory pathologist's diagnosis and to gross necropsy findings for the liver for each animal. Some changes in terminology were made in the original diagnosis for ease of data entry (see page 2 of PRP report). The results of this review are in Appendix A of the submission. The Pathology Review Panel (PRP) examined slides of liver (blind) from animals representing all groups and both sexes, although not all liver tumors were examined by PRP. All discrepancies in diagnosis of proliferative lesions in the liver between the Chairperson and the laboratory pathologist, as well as other findings for which the Chairperson agreed with the original diagnosis were presented to the PRP. Each proliferative lesion presented to the PRP was discussed and re-examined if necessary. A consensus diagnosis was reached when there was at least 3 out of 5 agreements. With regard to nonneoplastic hepatic lesions, a spectrum of these was examined by the PRP, which were representative of compound-related lesions identified originally and/or by the Chairperson. The purpose of this latter review was to reach a consensus on the type(s) of compound-related nonneoplastic lesions and to characterize these more completely than was done by the original pathologist.

Contractor's Analysis: The Chairperson identified an "unusual toxic lesion, which was diagnosed as peliosis hepatis, parenchymal form according to the description of Bannasch (1985)." The PRP concurred with this and considered multifocal hepatocellular necrosis and vacuolar degeneration as possible components of this toxic change. It was stated that Bannasch cited an article by Ruebner et al.,(1970) that "fully characterized this toxic hepatocellular change as lytic necrosis." The Chairperson obtained this reference and re-examined all livers and identified all animals with lytic necrosis using the diagnostic criteria of Ruebner, et al. (presented in Appendix D).

The findings of the panel regarding hepatic toxicity are not at odds with the original review, which also determined that the test material caused toxic lesions in the liver. However, with respect to the Registrant's contention that the liver tumors occurred only at doses that were hepatotoxic, TB II notes that the majority of the animals displaying lytic necrosis, which the Registrant equates to severe liver toxicity, did not display liver tumors (see below

and Appendix 1).

	Adenomas	Carcinomas	Lytic necrosis
Control [N] Males [99] Females [97]	5 [5]* 0	2 [2] 0	0 3 [3]
5 ppm Males [50] Females [50]	3 [6] 0	1 [2] 0	1(a)* [2] 1 [2]
15 ppm Males [49] Females [49]	4 [8] 1 [2]	3 [6] 0	4 [8] 7(1a) [14]
100 ppm Males [50] Females [49]	11(2a+c) [18] 1 [2]	6(2a+c) [12] 1 [2]	26(2a+c,5a,1c) 19(1c) [39]
200 ppm Males [50] Females [50]	11(3a+c) [16] 5(1a+c) [8]	6(3a+c) [12] 9(1a+c) [18]	39(3a+c,7a,1c) 21(1a+c,3c,1a)

* ( )# of animals with tumor [a-adenoma; c-carcinoma; a+c-both] and lytic necrosis

* [%]; lytic necrosis in 100 ppm males [52]; 200 ppm males [78]; 200 ppm females [42]

Following an outside peer review of microslides of the liver, the Registrant concluded that Cyproconazole induced hepatocellular tumors that were primarily benign in the two highest dose groups of male (100, 200 ppm) and in the highest dose group of female (200 ppm) CD-1 mice. Additionally, the two highest dose groups of both sexes had statistically significant increases in the incidence of lytic necrosis of the liver, which occurred over the course of the study and apparently was not life-threatening, since treated animals of both sexes survived longer than the controls. The Registrant stated that the most important observation of the outside peer review was that the "liver cell damage was present at termination and, therefore, must have occurred throughout the lifespans of the animals. Such a degenerative process in the liver invariably results in increased regenerative cellular proliferation, and the important role of cellular proliferation in tumor development is well recognized[2]. At low, non-toxic doses, there would be no increase in cell proliferation to promote tumor development."

Statistical analyses of the liver tumor incidence were presented (Tables 3 and 4, copies appended), and the Registrant concluded that since the "vast majority of these tumors were benign, were found at terminal sacrifice, and were not life-threatening (exposed animals of both sexes survived longer than controls), the

incidental tumor test was considered the more appropriate statistical test for these data." NOTE: This is not different from the analysis (Peto) performed by the Agency. When adjusted for survival (incidental tumor test), statistically significant increases in adenomas or in the combined tumors in males occurred at the 100 ppm dose only; the incidence of carcinomas in males not significantly increased at any dose. In females, the incidence of adenomas, carcinomas, and combined tumors was significantly increased above control at the high dose only. The occurrence of these tumors in only the high dose groups was said to correspond with the incidence of lytic necrosis, which was significantly increased in males at 15, 100, and 200 ppm and in females at 100 and 200 ppm (Table 5, copy attached). The PRP postulated that the tumors observed are secondary to the cytotoxicity observed and, if that was the primary mechanism of tumor production found in the high-dose groups (males), then the response at 15 ppm (significantly increased incidence of lytic necrosis in the absence of a positive tumor response) strongly suggests that a certain amount of cumulative organ damage may be necessary before these tumors are manifested. Similar observations were advanced for the females; no significant increases in either adenoma or carcinoma occurred at doses of 100 ppm and lower. Lytic necrosis was detected in females in the control group at an age-adjusted rate of 20%, and no significant increase in tumor production was observed even in the presence of lytic necrosis in approximately 70% (age-adjusted) of the 100 ppm group, which suggested to the Registrant that if the underlying basis for tumor production is cytotoxicity, then an accumulation of tissue damage precedes tumor production. However, TB II points out that if this were true, one would expect to find lytic necrosis in those animals displaying the tumors, which was not always the case in this study. For example, of the high-dose females displaying tumors, only 38% displayed lytic necrosis. In males, 79% of those with liver tumors displayed lytic necrosis.

It was concluded (by the Registrant/contractor) that the induced tumors appear to be the result of promotion of spontaneously initiated cells, given the lack of genotoxicity (according to the Registrant) and the occurrence of tumors only at doses that were hepatotoxic. It is further concluded that the tumor data are not suitable for quantitative risk assessment.

Comment: The differences in tumor incidence between that of the original report (used by the EPA Peer Review Committee) and that reported by the contractor are minor (see tables below). NOTE: Data reported as Sandoz is as reported by the contractor; PRP is as reported for the Pathology Review Panel; EPA PR was from the data submitted in the original review.

MALE ADENOMAS

Dose ppm	0	5	15	100	200
Sandoz	6/98	4/50	5/49	12/50	12/50
PRP	6/98	3/50	4/49	12/50	11/50
EPA PR	6/92	4/49	5/48	12/47	12/48

MALE ADENOMAS/CARCINOMAS combined

Dose ppm	0	5	15	100	200
Sandoz	6/98	4/50	8/49	14/50	13/50
PRP	7/98	4/50	7/49	15/50	14/50
EPA PR	6/92	4/49	8/48	15/47	13/48

FEMALE ADENOMAS

Dose ppm	0	5	15	100	200
Sandoz	0/97	0/50	0/49	0/49	6/50
PRP	0/97	0/50	1/49	2/49	6/50
EPA PR	0/61	0/34	0/28	2/41	6/39

FEMALE ADENOMAS/CARCINOMAS combined

Dose ppm	0	5	15	100	200
Sandoz	0/97	0/50	0/49	0/49	13/50
PRP	0/97	0/50	1/49	2/49	13/50
EPA PR	0/69	0/41	0/31	2/43	13/40

It is to be noted that the tables of tumor incidence in the two reports are in error (do not reflect the findings listed in Appendices A and D) with respect to the 100 ppm female group for both adenomas and carcinomas, and the tumor incidence of the original report for this group is incorrectly listed. In Table 1 (page 33 of the Evaluation prepared by Sandoz, which lists tumor incidence of the original report), 0/49 is listed for both the number of adenomas and carcinomas in this group. Appendix A lists both Animal #'s 353 and 375 with an adenoma (Primary Study). Table 2 of the Pathology Review Panel report (page 10) and Table 2 of Sandoz's evaluation (page 34) list the incidence of adenomas as 2/49 and carcinomas as 0/49. Appendix A (page 52) and Appendix D (page 74) both list an adenoma for Animal #375 (female - 100 ppm); Animal #353 is listed in both Appendix A (page 48) and D (page 69) as having a carcinoma. Additionally, Table 5 should have been

cited as presenting the incidence of lytic necrosis (not Table 2) on page 5 of the contractor's evaluation.

RAT STUDY

With regard to the issue of MTD, the consultant reiterates the same arguments submitted previously (see TB II memo dated 3/20/91), as well as a general discussion of MTD. The main argument focuses on the percent body-weight gain for both sexes in the subchronic study [decrement in female (12.5%) and male (7.4%)]. When the liver weight is subtracted from the total body weight, the percentage decreases become 13.3 for females and 7.75 for males. In the Prodiamine Peer Review, which the Registrant contends is similar to the current situation, the 2-year rat study was considered to have reached an MTD, based on body-weight gain decrement of 14.3% (males) and 8.4% (females) at a dose of 3200 ppm reached in that study. The subchronic study on Prodiamine had tested dose levels of 400, 1200 and 4000 ppm, where the high dose displayed body-weight gain decrements of 13% (males) and 10 to 15% in females. Based on this significant decrease, the high dose for the carcinogenicity study on Prodiamine was set at 3200 ppm. This situation differs from the Cyproconazole situation in that the body-weight gain decrement in the Prodiamine subchronic study was observed in both sexes and the high-dose chosen for the long-term study also produced a body-weight gain decrement, which, although less than a 10% decrement in females, was accompanied by a compound-related increase in the incidence of thyroid tumors; no effects were observed in the Cyproconazole long-term study.

Issues ignored in their arguments include the fact that in the subchronic study, the liver effects (histological changes) were reversible, there was a lack of consistent liver enzyme effects, and no life-threatening histopathological lesions were observed. Additionally, there is nothing "magic" in the 10% figure stated in the MTD document, which in fact states should reach 10-15%. What determines whether a particular dose is adequate is the total picture; i.e., body-weight gain deficit, organ weight effects accompanied by toxic lesions, not adaptive lesions. The recovery phase of the rat subchronic study clearly showed that the liver lesions observed were adaptive measures. There was no demonstration of a spectrum of histopathological change in the liver of rats in that study. As stated in the MTD document quoted by the consultant, in the past chronic studies on various hepatotoxins were performed at doses based on organ weight increases, cloudy swelling and vacuolation, alone or in combination and the doses were not adequate, as in the case of Cyproconazole. These lesions are often not life-threatening. The lesions displayed in the Cyproconazole subchronic study were vacuolated hepatocytes and enlarged hepatocytes, which were not observed after the recovery period. Although the high dose in the long-term study was 30 ppm higher than that in the subchronic study, given the minimal toxicity observed and the reversibility of the liver effects, the rats would

have tolerated higher doses. The high dose in the 4-week study was 1000 ppm, which did not cause any deaths or treatment-related symptoms, although there was a significant decrease in body-weight gain at this level (and food wastage). The next highest dose in that study was 300 ppm.

The Registrant's evaluation of the carcinogenicity/mutagenicity data, as well as this review of that data will be presented to the HED Peer Review Committee for consideration in the near future.

APPENDIX 1

Identity of animals displaying liver tumors/lytic necrosis

Animal #	Week of death	Tumor Type	Lytic Necrosis	Necrosis MF/HC	Peliosis Hepatis
2	81	-	-	X*	-
9	80	adenoma	-	-	-
39	83T	adenoma	-	-	-
40	83T	adenoma	-	-	-
45	76	carcinoma	-	-	-
96	89	-	-	X*	-
111	56	carcinoma	-	-	-
113	82T	adenoma	X	-	*
140	75	adenoma	-	-	-
146	83T	adenoma	-	-	-
151	89T	-	X	-	*
164	89T	-	-	*	-
183	77	-	-	X*	-
207	79	adenoma	-	-	-
211	82T	-	X	-	-
215	82T	-	X	-	-
224	82T	adenoma	-	-	-
225	70	-	X	*	-
233	83T	adenoma	-	-	-
235	82T	-	-	-	*
238	83T	adenoma	-	-	-
239	83T	carcinoma	-	-	-
243	79	carcinoma	-	-	-
245	83T	-	X	-	-
249	83T	carcinoma	-	-	-
254	90T	-	X	-	-
264	90T	-	X	-	-
265	90T	-	X	*	-
270	74	-	X	-	-
271	87	-	X	-	-
275	67	-	-	-	-
285	90T	-	X	-	-
286	90T	-	-	*	-
289	91T	adenoma	X	-	-
301	82T	adenoma	X	-	-
303	68	carcinoma	-	-	-
304	79	-	X	-	-
305	69	-	X	*	*
307	87T	carcinoma adenoma	X	-	-
308	82T	adenoma	X	-	*
311	82T	-	X	-	-
312	82T	-	X	-	-
314	73	-	X	-	-
315	82T	-	X	-	-
317	82T	adenoma	X	-	-
322	82T	adenoma	-	-	-
323	82T	-	X	*	*
324	82T	adenoma	X	-	-
326	72	-	X	-	-

327	83T	adenoma	-	-	-
328	83T	-	X	-	-
331	83T	adenoma	-	-	-
333	73	carcinoma	-	-	-
336	83T	carcinoma	X	-	-
337	83T	carcinoma adenoma	X	-	-
338	71	-	X	-	-
339	83T	-	X	-	*
340	67	-	X	-	-
341	57	adenoma	-	-	-
342	83T	-	X	-	-
343	83T	carcinoma	-	-	-
344	83T	adenoma	X	*	-
345	83T	-	X	-	*
346	83T	-	X	-	-
347	55	-	X	*	-
348	83T	-	X	-	-
349	83T	-	X	-	-
351	53	-	X	-	-
353	90T	carcinoma	X	-	-
356	90T	-	X	-	*
357	90T	-	X	-	*
359	90T	-	X	-	-
361	90T	-	X	-	*
366	90T	-	X	-	-
371	90T	-	X	-	-
375	90T	adenoma	-	-	-
377	91T	-	X	-	-
379	91T	-	X	-	-
381	90T	-	X	-	-
382	91T	-	X	-	-
383	91T	-	X	-	-
384	89	-	X	-	*
387	91T	-	X	-	-
389	91T	-	X	-	*
391	91T	-	X	-	*
393	91T	-	X	-	-
395	91T	-	X	-	*
401	82T	carcinoma	-	-	-
402	82T	adenoma	X	-	-
404	76	-	X	-	-
405	81	-	X	-	-
406	82T	adenoma	X	-	-
407	71	carcinoma	X	-	-
409	82T	-	X	-	-
410	82	-	X	-	-
411	82T	-	X	-	-
412	82T	-	X	-	-
413	82T	-	X	-	-
414	78	-	X	*	*
415	82T	-	X	-	*

417	82T	-	X	-	*
418	82T	-	X	-	*
419	61	-	X	-	-
420	82T	-	X	*	-
421	82T	-	X	-	*
422	82T	adenoma	-	-	-
423	82T	adenoma	X	*	*
424	62	-	X	-	*
426	83T	-	X	-	-
427	83T	carcinoma adenoma	X	-	*
428	82T	carcinoma adenoma	X	*	-
429	83T	-	X	-	-
432	83T	-	X	-	-
433	83T	-	X	*	*
435	82T	-	X	*	*
436	83T	-	X	-	-
437	83T	adenoma	X	-	*
438	82T	-	X	-	-
439	83T	-	X	-	-
440	83T	adenoma	X	*	*
441	83T	-	X	*	*
442	76	carcinoma	-	-	-
443	83T	-	X	-	*
445	83T	-	X	-	-
446	66	-	X	-	-
447	82	adenoma	X	-	-
448	83T	-	X	-	*
449	83T	carcinoma adenoma	X	-	*
450	83T	adenoma	X	-	-
451	90T	adenoma	-	-	-
453	89T	-	X	-	-
454	90T	-	X	-	-
455	90T	-	X	-	-
456	89T	adenoma	-	-	-
457	83	carcinoma	-	-	-
460	89T	-	X	-	*
461	90T	-	X	-	-
462	90T	carcinoma adenoma	X	-	-
463	90T	-	X	-	*
464	80	adenoma	-	-	-
465	90T	carcinoma	X	-	*
467	76	carcinoma	-	-	-
468	82	carcinoma	X	-	-
470	38	-	-	X*	-
473	91T	carcinoma	-	X*	-
474	85	carcinoma	-	-	-
476	91T	-	X	-	-
478	90T	-	-	X*	

479	83	adenoma	X	-	-
482	91T	-	X	-	-
484	89	carcinoma	-	-	-
486	91T	-	X	-	-
487	86	-	X	-	*
488	91T	-	X	-	-
491	91T	-	X	-	*
493	88	-	X	-	*
495	91T	-	X	-	*
496	90T	-	X	-	-
498	87	carcinoma	X	*	-
500	91T	-	X	-	-
509	82T	carcinoma	-	-	-
518	82T	adenoma	-	-	-
536	82T	adenoma	-	-	-
573	91T	-	-	X*	-
575	91T	-	X	-	*
583	91T	-	X	-	*
586	86	-	-	-	*
590	90T	-	X	-	-
596	74	-	-	X*	-

Data from Appendix D (tumors confirmed with Appendix A); "X" data found in Appendix D; "*" data found in Appendix A; Lytic necrosis was cited only in Appendix D; Peliosis hepatis was cited only in Appendix A; Vacuolar degeneration (considered a component of the unusual toxic change identified by Chairperson) was not listed in either appendix.

TABLE 1

Incidence of Hepatocellular Tumors in Male and Female
CD-1 Mice Given Cyproconazole in the Diet
Original Pathology Report

	0	5 ppm	15 ppm	100 ppm	200 ppm
MALES					
Adenomas	6/98	4/50	5/49	12/50	12/50
Carcinomas	0/98	0/50	3/49	3/50	1/50
Total	6/98	4/50	8/49	14/50	13/50
FEMALES					
Adenomas	0/97	0/50	0/49	2/49	6/50
Carcinomas	0/97	0/50	0/49	0/49	7/50
Total	0/97	0/50	0/49	0/49	13/50

TABLE 2

Incidence of Hepatocellular Tumors in Male and Female
CD-1 Mice Given Cyproconazole in the Diet
Pathology Peer Review

	0	5 ppm	15 ppm	100 ppm	200 ppm
MALES					
Adenomas	6/98	3/50	4/49	12/50	11/50
Carcinomas	1/98	1/50	3/49	4/50	3/50
Total	7/98	4/50	7/49	15/50	14/50
FEMALES					
Adenomas	0/97	0/50	1/49	2/49	6/50
Carcinomas	0/97	0/50	0/49	0/49	7/50
Total	0/97	0/50	1/49	2/49	13/50

TABLE 3

HEPATOCELLULAR TUMORS IN MALE CD-1 MICE FROM
THE CHRONIC DIETARY STUDY OF SAN 619F

MALE MICE ADENOMA AND CARCINOMA - MERGED CONTROLS

	CONTROL2	LOW DOSE	MEDIUM1 DOSE	MEDIUM2 DOSE	HIGH DOSE
Overall Incidence	7/ 98 (7%)	4/ 50 (8%)	7/ 49 (14%)	15/ 50 (30%)	14/ 50 (28%)
Adjusted Incidence	18.1%	14.8%	22.7%	45.4%	34.8%
Terminal Incidence	5/ 35 (14%)	2/ 20 (10%)	5/ 28 (18%)	12/ 29 (41%)	12/ 38 (32%)
Life Table Test	P= .019	P= .613	P= .425	P= .010	P= .085
Incidental Tumor Test	P= .002	P= .119	P=1.000	P= .007	P= .186
Armitage Trend Test	P= .000				
Fisher Exact Test		P= .544	P= .138	P= .000	P= .001

MALE MICE ADENOMA - MERGED CONTROLS

	CONTROL2	LOW DOSE	MEDIUM1 DOSE	MEDIUM2 DOSE	HIGH DOSE
Overall Incidence	6/ 98 (6%)	3/ 50 (6%)	4/ 49 (8%)	12/ 50 (24%)	11/ 50 (22%)
Adjusted Incidence	15.3%	13.0%	13.3%	39.3%	28.9%
Terminal Incidence	4/ 35 (11%)	2/ 20 (10%)	3/ 28 (11%)	11/ 29 (38%)	11/ 38 (29%)
Life Table Test	P= .032	P= .423	P= .474	P= .031	P= .176
Incidental Tumor Test	P= .010	P= .415	P= .400	P= .014	P= .094
Armitage Trend Test	P= .000				
Fisher Exact Test		P= .642 N	P= .441	P= .003	P= .006

MALE MICE CARCINOMA - MERGED CONTROLS

	CONTROL2	LOW DOSE	MEDIUM1 DOSE	MEDIUM2 DOSE	HIGH DOSE
Overall Incidence	1/ 98 (1%)	1/ 50 (2%)	3/ 49 (6%)	4/ 50 (8%)	3/ 50 (6%)
Adjusted Incidence	2.9%	2.0%	9.9%	11.4%	7.2%
Terminal Incidence	1/ 35 (3%)	0/ 20 (0%)	2/ 28 (7%)	2/ 29 (7%)	1/ 38 (3%)
Life Table Test	P= .242	P= .624	P= .228	P= .105	P= .276
Incidental Tumor Test	P= .095	P= .635	P= .155	P= .060	P= .149
Armitage Trend Test	P= .081				
Fisher Exact Test		P= .563	P= .108	P= .045	P= .112

TABLE 4

HEPATOCELLULAR TUMORS IN FEMALE CD-1 MICE FROM
THE CHRONIC DIETARY STUDY OF SAN 619F

FEMALE MICE ADENOMA AND CARCINOMA - MERGED CONTROLS

	CONTROL2	LOW DOSE	MEDIUM1 DOSE	MEDIUM2 DOSE	HIGH DOSE
Overall Incidence	0/ 97 (0%)	0/ 50 (0%)	1/ 49 (2%)	2/ 49 (4%)	13/ 50 (26%)
Adjusted Incidence	.0%	.0%	4.3%	5.4%	34.3%
Terminal Incidence	0/ 44 (0%)	0/ 26 (0%)	1/ 23 (4%)	2/ 37 (5%)	6/ 30 (20%)
Life Table Test	P= .000	P=1.000	P= .371	P= .201	P= .000
Incidental Tumor Test	P= .000	P=1.000	P= .345	P= .157	P= .000
Armitage Trend Test	P= .000				
Fisher Exact Test		P=1.000	P= .336	P= .111	P= .000

FEMALE MICE ADENOMA - MERGED CONTROLS

	CONTROL2	LOW DOSE	MEDIUM1 DOSE	MEDIUM2 DOSE	HIGH DOSE
Overall Incidence	0/ 97 (0%)	0/ 50 (0%)	1/ 49 (2%)	2/ 49 (4%)	6/ 50 (12%)
Adjusted Incidence	.0%	.0%	4.3%	5.4%	17.3%
Terminal Incidence	0/ 44 (0%)	0/ 26 (0%)	1/ 23 (4%)	2/ 37 (5%)	3/ 30 (10%)
Life Table Test	P= .000	P=1.000	P= .371	P= .201	P= .005
Incidental Tumor Test	P= .000	P=1.000	P= .345	P= .157	P= .003
Armitage Trend Test	P= .000				
Fisher Exact Test		P=1.000	P= .336	P= .111	P= .001

FEMALE MICE CARCINOMA - MERGED CONTROLS

	CONTROL2	LOW DOSE	MEDIUM1 DOSE	MEDIUM2 DOSE	HIGH DOSE
Overall Incidence	0/ 97 (0%)	0/ 50 (0%)	0/ 49 (0%)	0/ 49 (0%)	7/ 50 (14%)
Adjusted Incidence	.0%	.0%	.0%	.0%	19.6%
Terminal Incidence	0/ 44 (0%)	0/ 26 (0%)	0/ 23 (0%)	0/ 37 (0%)	3/ 30 (10%)
Life Table Test	P= .000	P=1.000	P=1.000	P=1.000	P= .002
Incidental Tumor Test	P= .000	P=1.000	P=1.000	P=1.000	P= .001
Armitage Trend Test	P= .000				
Fisher Exact Test		P=1.000	P=1.000	P=1.000	P= .000

TABLE 5

LYTIC NECROSIS IN CD-1 MICE FROM THE CHRONIC
DIETARY STUDY OF SAN 619F

MALE MICE LYTIC NECROSIS - MERGED CONTROLS

	CONTROL2	LOW DOSE	MEDIUM1 DOSE	MEDIUM2 DOSE	HIGH DOSE
Overall Incidence	0/ 99 (0%)	1/ 50 (2%)	4/ 49 (8%)	26/ 50 (52%)	39/ 50 (78%)
Adjusted Incidence	.0%	5.0%	12.7%	71.1%	86.6%
Terminal Incidence	0/ 35 (0%)	1/ 20 (5%)	3/ 28 (11%)	19/ 29 (66%)	32/ 38 (84%)
Life Table Test	P= .000	P= .388	P= .035	P= .000	P= .000
Incidental Tumor Test	P= .000	P= .388	P= .020	P= .000	P= .000
Armitage Trend Test	P= .000				
Fisher Exact Test		P= .336	P= .011	P= .000	P= .000

FEMALE MICE LYTIC NECROSIS - MERGED CONTROLS

	CONTROL2	LOW DOSE	MEDIUM1 DOSE	MEDIUM2 DOSE	HIGH DOSE
Overall Incidence	3/ 97 (3%)	1/ 50 (2%)	7/ 49 (14%)	19/ 49 (39%)	21/ 50 (42%)
Adjusted Incidence	6.8%	3.8%	27.3%	49.7%	61.5%
Terminal Incidence	3/ 44 (7%)	1/ 26 (4%)	5/ 23 (22%)	18/ 37 (49%)	17/ 30 (57%)
Incidental Tumor Test	P= .000	P=1.000	P= .393	P= .169	P= .022
Armitage Trend Test	P= .000				
Fisher Exact Test		P= .580 N	P= .017	P= .000	P= .000

7. Life Table Test