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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

TXR No.: 0054599

MEMORANDUM

DATE: May 17, 2007

SUBJECT: PYRASULFOTOLE: Report of the Cancer Assessment Review Committee
PC Code: 000692

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Robert Mitkus, Toxicologist (RAB1)
Jennifer Tyler, Risk Assessor (RAB1)
Health Effects Division (7509P)

Joanne Miller, PM
Herbicide Branch, Registration Division (7505P)

The Cancer Assessment Review Committee met on April 4, 2007 to evaluate the carcinogenic potential of Pyrasulfotole. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher
Y. Woo

05/23/2007
Received in
RRC
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CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

PYRASULFOTOLE

PC CODE 000692

FINAL

May 17, 2007

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: Robert Mitkus, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Karlyn Bailey

Lori Brunsman, Statistician

William Burnam, Chair

Marion Copley

Ray Kent

Mary Manibusan

Nancy McCarroll

Jess Rowland

Yin-Tak Woo — See attached

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist — See attached

OTHER ATTENDEES: PMRA (Canada): Catherine Adcock, Steve Wong, Kim Low, Carmen Chung; APVMA (Australia): Julian O'Dea; EPA: Melissa Panger (EFED), Megan Thynge (EFED), Guruva Reddy (HED), Lisa Austin (HED), PV Shah (HED)

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

On April 4, 2007, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met for the first time to evaluate the carcinogenic potential of pyrasulfotole. The toxicological database is being jointly reviewed by Australian (APVMA), Canadian (PMRA), and American (EPA) regulators.

Robert Mitkus of Registration Action Branch 1 presented the chronic toxicity/carcinogenicity study in Wistar rats and the carcinogenicity study in C57BL/6 mice. In the chronic toxicity/carcinogenicity study, pyrasulfotole (95.7% a.i.) was administered in the diet to 75 six-week-old Wistar Rj:WI (IOPS HAN) rats/sex/group at dose levels of 0, 25, 250, 1000, or 2500 ppm (equivalent to 0/0, 1.0/1.4, 10/14, 41/57, or 104/140 mg/kg bw/day in males/females) for 24 months. Animals were sacrificed at 6 (10/dose group), 12 (10/dose group), and 24 months (55/dose group). In the carcinogenicity study, pyrasulfotole (95.7% w/w a.i.) was administered in the diet to C57BL/6J mice (50/dose) at doses of 0, 100, 1000, or 4000 ppm for males. Groups of 50 females/group received 0, 100, 1000, or 6000 ppm for the first 10 weeks. The high dose in females was reduced to 4000 ppm from week 11 onwards, because it was considered excessive due to increased mortality. The concentrations resulted in doses of 0/0, 13.6/16.7, 137/168, or 560/713 mg/kg/day (M/F) for up to 78 weeks. Additionally, an interim group of 10 mice/sex/dose were treated similarly for up to 52 weeks and then sacrificed. He also presented information on mutagenicity, structure activity relationships, and mode of action data.

The CARC concluded the following:

Carcinogenicity

Rats

- There were no treatment-related increases in tumors in female Wistar rats.

- An increased incidence of corneal tumors (squamous cell papilloma and carcinoma) was observed in males at the high dose (2500 ppm) only. The incidences of these rare tumors observed in two males were not analyzed statistically, since they were so low individually (1/55 each, 2500 ppm vs 0/55, control) and when combined (2/55, 2500 ppm vs 0/55, control). However, the incidence did exceed the historical control incidence of these tumors (0/403 in males) in 7 studies conducted from 2000-2005 at Bayer CropScience Centre de Recherche Sophia Antipolis. In addition, corneal hyperplasia, a preneoplastic lesion, was seen at the high dose. **Therefore, the CARC concluded that these rare corneal tumors were treatment-related.**

- Adequacy of Dosing: Dosing at the high dose was considered adequate, but not excessive, in male and female Wistar rats. This was based on decreased body weight/body weight gain and non-neoplastic lesions of the eyes, liver, pancreas, thyroid and kidney seen at the high dose. In males, body weight in males was statistically decreased during the study at 2500 ppm (≤12%). Body weight gains were decreased 7-16%, except late in the study (days 540-708) when body

weights declined in all groups including controls. There were also indications of depressed final body weights (≤8%; NSS) and body weight gains (12%) in the female rats at the high dose. Other findings which support that the high dose was adequate include increases in histopathology of the eyes, pancreas, thyroid gland, and kidneys of both sexes which were observed at >25 ppm, as well as increases in centrilobular hepatocellular hypertrophy in males at ≥250 ppm along with minor increases in cholesterol/triglyceride levels. Mortality was increased to 72.7% ($p<0.05$) at 24 months in high-dose males. However, mortality at this dose was similar to that observed at 25 ppm (69.1%; NSS) and, therefore, not considered excessive.

Mice

- Male C57BL/6 mice had statistically significant trends, and significant pair-wise comparisons of the 4000 ppm dose group with the controls, for urinary bladder transitional cell carcinomas (8/34 (24%) vs 0/47, controls), and papillomas and carcinomas combined (11/34 (32%) vs 0/47, controls), all at $p < 0.01$. There was also a statistically significant trend for urinary bladder transitional cell papillomas at $p < 0.05$. In addition, although there was only one urethral transitional cell carcinoma at the high dose (1/24 (4%)), there was a statistically significant trend at $p < 0.05$ due to increased mortality at the high dose. This urethral transitional cell carcinoma should be considered the same tumor type as the transitional cell carcinomas in the urinary bladder. No tumors were seen at 100 or 1000 ppm. The incidence of tumors at the high dose exceeded the historical control data for bladder tumors in males (0/394) across 5 studies (2000-2005) performed at Bayer CropScience Centre de Recherche Sophia Antipoli (CRSA). **Therefore, the CARC considered these tumors at the high dose to be treatment related.**

- Female mice had statistically significant trends for urinary bladder transitional cell papillomas, carcinomas, and papillomas and carcinomas combined, all at $p < 0.01$. There were significant pair-wise comparisons of the 4000 ppm dose group with the controls for both urinary bladder transitional cell papillomas (2/19 (11%) vs 0/35, controls) and carcinomas (2/19 (11%) vs 0/35, controls), both at $p < 0.05$, and for urinary bladder transitional cell papillomas and carcinomas combined (4/19 (21%)) vs 0/35, control) at $p < 0.01$. The incidence of the tumors at the high dose exceeded the historical control incidence for bladder tumors in females (0/380 across 5 studies performed at CRSA). **Therefore, the CARC considered these tumors at the high dose to be treatment related.**

- Adequacy of Dosing: The CARC considered the high dose of 4000 ppm to be excessive in both sexes because of significantly increased mortality in males (53% vs 16% in controls) and females (62% vs 30% in controls), much of which occurred in the first year of the study. The increased mortality was due to the presence of urinary bladder stones. The CARC could not dismiss these rare bladder tumors, but their relevance to human risk was lessened because these tumors were seen only at the dose where death, stones, and bladder hyperplasia were evident. In addition, dose selection for the long term study was reasonable based on the results of the 90-day mouse study where no effects were seen at 3000 ppm.

Mutagenicity

The parent compound, pyrasulfotole and its benzoic metabolite, AE B197555, do not pose a mutagenic concern.

Structure Activity Relationship

Pyrasulfotole and a variety of other structurally related herbicides (tembotrione, mesotrione, NTBC, topramezone, isoxaflutole) are capable of inhibiting HPPD to various degrees. With the exception of isoxaflutole (which does not contain a hydroxy group on the 5-membered ring), all these herbicides either contain a beta-diketo structural moiety or can be converted to a beta-diketo moiety via keto-enol tautomerization. Both pyrasulfotole and tembotrione have been shown to induce rare corneal tumors in male rats but not in female rats or mice. NTBC has been shown to induce corneal lesions in male rats and beagle dogs but not in mice, rabbits and monkeys. Mesotrione was classified by HIARC in 2001 as "not likely to be carcinogenic to humans" by all route of exposure based upon lack of evidence of carcinogenicity in rats and mice. Topramezone was classified by CARC in 2005 as "not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis" based on treatment-related increases in thyroid follicular cell tumors in male and female rats. There was some evidence of corneal hyperplasia but no tumors. In 1996, isoxaflutole was classified as "likely to be a human carcinogen" based on increases in liver tumors in both sexes of mice and rats and increases in thyroid follicular cell tumors in male rats. There was no significant concern for mutagenicity for any of these herbicides.

Mode of Action

Corneal Tumors (male rat): While the CARC considered it was biologically plausible for corneal tumors to result from a nongenotoxic mode of action that was secondary to corneal inflammation and regenerative hyperplasia caused by tyrosine, inadequate data were available to firmly support this mode of action.

Bladder tumors (mice): While the CARC considered that it was biologically plausible for the bladder tumors in male and female mice to be the result of a nongenotoxic proliferative mechanism due to the concurrent presence of secondary inflammation and hyperplastic findings in the urinary bladder, induced by the urinary stones, inadequate data were available to firmly support this mode of action. However, it is noted that there was dose and temporal concordance among putative key events that were observed in two mouse toxicology studies. In addition, in the carcinogenicity study in mice, bladder tumors were observed only at that dose at which urinary bladder stones or concretions were also observed.

Classification and Quantification of Carcinogenic Potential

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified pyrasulfotole as "Suggestive Evidence of Carcinogenic Potential". This was based on the following weight of evidence considerations: 1) Two male rats had rare treatment-related corneal tumors at the highest dose tested (2500 ppm [104/140 mg/kg/day, M/F]), which was a dose associated with widespread corneal inflammation, hyperplasia, metaplasia, neurovascularization and atrophy; 2) Treatment-related urinary bladder transitional cell tumors were seen in male and female mice only at the highest dose tested (4000 ppm [560/713 mg/kg/day, M/F]). The highest dose tested in mice was considered to be excessive due to increased mortality caused by the presence of urinary bladder stones. The fact that these tumors were seen only in the presence of increased mortality, along with hyperplasia and stone formation, lessens their relevance for human risk; 3) While the CARC noted the progression of non-neoplastic related lesions in both the rats and mice and acknowledged biologically plausible non-genotoxic modes of action for both the corneal tumors and the bladder tumors, they concluded that there was insufficient data at this time to fully support the modes of action; 4) There is no mutagenicity concern for pyrasulfotole.

Quantification of carcinogenic potential is not required. The chronic Reference Dose (cRfD) of 0.01 mg/kg/day, derived from the NOAEL of 1.0 mg/kg/day in rats along with an uncertainty factor of 100, would be protective of both non-cancer and cancer effects.

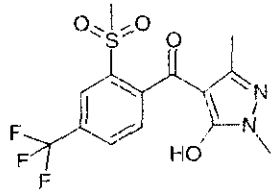
I. INTRODUCTION

On April 4, 2007, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met for the first time to evaluate the carcinogenic potential of pyrasulfotole. The toxicological database is being jointly reviewed by Australian (APVMA), Canadian (PMRA), and American (EPA) regulators.

II. BACKGROUND INFORMATION

Pyrasulfotole is a post-emergence benzylpyrazole herbicide that is proposed to be used on several broadleaf species of weeds in various cereal crops.

Chemical Name:	Pyrasulfotole
IUPAC Name:	(5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]methanone
Chemical Formula:	$C_{14}H_{13}F_3N_2O_4S$
Chemical Structure:	



CAS Registry #:	365400-11-9
PC CODE:	000692

Pyrasulfotole is an inhibitor of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD). In mammals, HPPD catalyzes the reversible conversion of 4-hydroxyphenylpyruvate (HPP) to homogentisate, primarily in the liver (Figure 1). Blockage of tyrosine catabolism at this point causes an increase in blood tyrosine concentrations beyond normal (tyrosinemia). Blockage of HPPD in plants leads to inhibition of photosynthesis; this phytotoxicity is the basis of the herbicidal action of HPPD inhibitors. Based on selective modification of the model HPPD inhibitor and triketone herbicide NTBC, chelation occurs between the enol tautomer of NTBC (or structurally related compounds) and a ferric iron (Fe^{2+}) bound to HPPD (Hanauske-Abel et al. 2002; Wu et al. 2002).

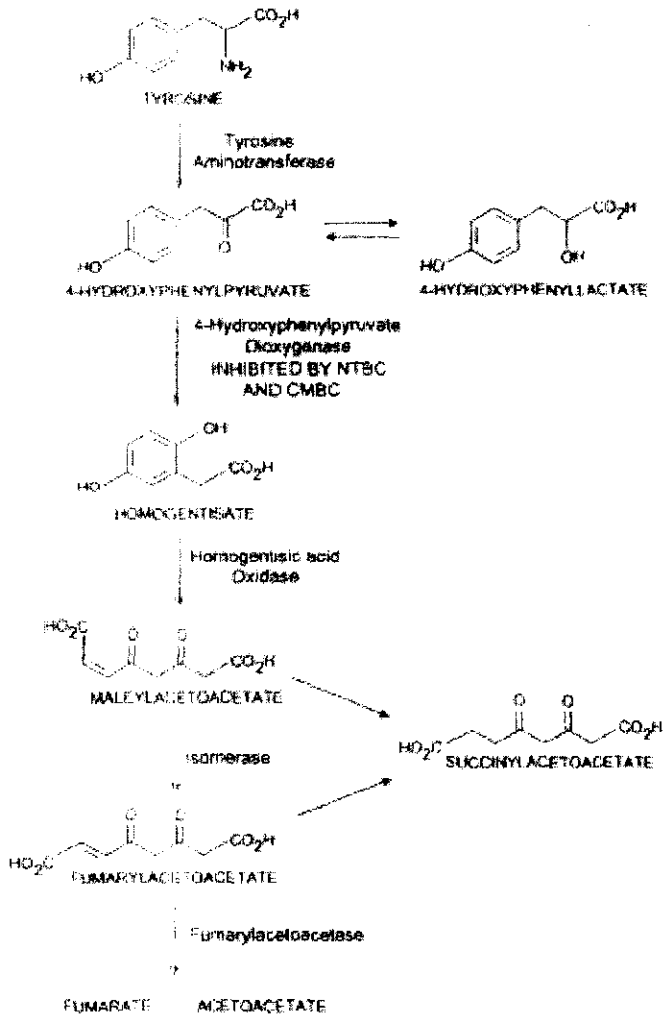


Figure 1. The pathway of mammalian tyrosine catabolism (Reproduced from Ellis et al 1995). Note: the conversion of tyrosine to 4-hydroxyphenylpyruvate by tyrosine aminotransferase is also reversible.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study (Rats)

Reference: Wason S. (2006). 6-Month toxicity, chronic toxicity and carcinogenicity study of AE 0317309 in the Wistar rat by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 02453, February 28, 2006. MRID 46801910.

A. Experimental Design

Pyrasulfotole (95.7% a.i.) was administered in the diet to 75 six-week-old Wistar Rj:WI (IOPS HAN) rats/sex/group at dose levels of 0, 25, 250, 1000, or 2500 ppm (equivalent to 0/0, 1.0/1.4, 10/14, 41/57, or 104/140 mg/kg bw/day in males/females) for 24 months. Animals were sacrificed at 6 (10/dose group), 12 (10/dose group), and 24 months (55/dose group).

B. Discussion of Tumor Data

Mortality

Mortality was statistically significantly increased to 72.7% in high-dose males at 24 months. While treatment-related, the increase in mortality did not compromise the validity of the study, since it was less than 75% (OPPTS 870.4300).

Table 1. Mortalities in male rats treated with pyrasulfotole

Month	Dose (ppm)									
	Males					Females				
	0	25	250	1000	2500	0	25	250	1000	2500
Mortality (N=55)										
6	1	1	0	1	4	0	0	0	0	0
12	2	6	2	2	8	2	1	0	1	0
24	30	38	25	29	40*	28	19	25	22	26
Mortality (%)										
6	1.3	1.3	0.0	1.3	5.3	0.0	0.0	0.0	0.0	0.0
12	3.1	9.2	3.1	3.1	12.3	3.1	1.5	0.0	1.5	0.0
24	54.5	69.1	45.5	52.7	72.7	50.9	34.5	45.5	40.0	47.3

*$p < 0.05$

Corneal Tumors

An increased incidence of corneal tumors was observed in high-dose males (2500 ppm; 104 mg/kg/day). The incidences of these rare tumors observed in two males were not analyzed statistically, since they were so low individually (1/55 each) and when combined (2/55). However, the incidence did exceed the historical control incidence of these tumors (0/403 in

males) in 7 studies conducted from 2000-05 at Bayer CropScience Centre de Recherche Sophia Antipolis under the current head of pathology. The registrant considered these tumors to be treatment-related and suggested that they resulted from corneal inflammation and regenerative hyperplasia due to tyrosinemia. Photos of the tumors are attached in the Appendix. Squamous cell corneal tumors were also observed in male rats treated for 2 years with the HPPD inhibitor tembotrione at 200 ppm (4/60) and 800 ppm (2/60). Ocular tumors were not seen when the HPPD inhibitors mesotrione, topramezone, and isoxaflutole were each tested in rats for two years at doses up to 190, 381.5, and 500 mg/kg/day, respectively.

Table 2. Male rats: Incidence of corneal tumors

Concentration (ppm):	25	250	1000	2500
Dose (mg/kg/day):	1	10	41	104
Tumor Type				
Squamous cell papilloma	0/55	0/55	0/55	1/55
Squamous cell carcinoma	0/55	0/55	0/55	1/55
Combined	0/55	0/55	0/55	2/55

No treatment-related tumors were observed in female rats.

C. Non-Neoplastic Histopathological Findings

Treatment-related, non-neoplastic microscopic findings were observed in the eyes, liver, pancreas, thyroid gland, and kidneys of both sexes at >25 ppm (Tables 3-7).

Eyes

In the eyes, the incidence of corneal inflammation was significantly increased at all time points in males at dietary concentrations of 250 ppm and above, and in females at all time points at 1000 and 2500 ppm. At 24 months, there was a slight increase (NSS) in corneal inflammation in males at 25 ppm (5%). The historical control range of unilateral and bilateral inflammation of the cornea is 0/60-3/59 (0-5%) in males and 0/60-2/60 (0-3%) in females in 7 studies conducted from 2000-05 at Bayer CropScience Centre de Recherche Sophia Antipolis under the current head of pathology. The incidences of corneal inflammation at ≥250 ppm were therefore outside

the historical control range. Regenerative hyperplasia of the cornea was increased in males at all time points at 250 ppm and above, and in females at all time points at 1000 and 2500 ppm. Neovascularization of the cornea was increased in males at 6, 12, and 24 months at 250 ppm and above, in females at 6 and 12 months at 1000 and 2500 ppm, and in females at 24 months at 250 ppm and above. At 24 months, there was an increase in males in the incidence of mucous metaplasia of the cornea at 250 ppm and above. Also at 24 months, corneal atrophy was increased in males at 250 ppm and above and in females at 1000 and 2500 ppm, and peripheral retinal atrophy was statistically significantly increased in both males and females at 250 ppm and above. The increase in corneal inflammation in males is likely a precursor event to the regenerative hyperplasia observed at this same dose.

Table 3. *Incidence of non-neoplastic microscopic findings in the eyes*

Finding	Dose (ppm)									
	Males					Females				
	0	25	250	1000	2500	0	25	250	1000	2500
6 months										
N examined	9	10	10	10	10	10	10	10	10	10
Inflammation, cornea, unilateral or bilateral	0	0	6	8	8	0	0	0	6	7
Hyperplasia, cornea, regenerative, unilateral or bilateral	0	0	5	8	7	0	0	0	5	6
Neovascularization, cornea, unilateral or bilateral	0	0	3	7	6	0	0	0	3	6
12 months										
N examined	10	10	9	10	8	9	10	10	9	10
Inflammation, cornea, unilateral or bilateral	0	0	6	9	8	0	1	0	5	7
Hyperplasia, cornea, regenerative, unilateral or bilateral	0	0	6	9	8	0	1	0	4	6
Neovascularization, corneal, unilateral or bilateral	0	1	5	8	8	0	1	0	4	7
24 months										
N examined	55	55	55	55	55	55	55	54	55	55
Inflammation, cornea, unilateral or bilateral	1	3	39**	49**	44**	0	1	2	28**	32**
Hyperplasia, cornea, regenerative, unilateral or bilateral	0	0	31**	38**	32**	1	0	2	24**	25**
Neovascularization, cornea, unilateral or bilateral	2	3	46**	49**	53**	0	0	13**	41**	42**
Vacuolation, cornea, focal	0	0	2	0	2	1	0	0	5	5
Metaplasia, mucous, cornea	0	0	2	9**	11**	0	0	0	0	0
Atrophy, cornea	0	0	11**	25**	24**	0	0	0	5*	6*

Finding	Dose (ppm)									
	Males					Females				
	0	25	250	1000	2500	0	25	250	1000	2500
Atrophy, retina, peripheral, unilateral or bilateral	2	3	17**	15**	17**	1	4	8*	20**	13**

*p<0.05; ** p< 0.01

Liver

At 6 months, centrilobular hepatocellular hypertrophy was increased in males at all doses and in females from 250 ppm onwards. However, at 12 and 24 months in males this finding was reported only from 250 ppm onwards. In females, there was no centrilobular hepatocellular hypertrophy at 12 months, and at 24 months it was only reported in one animal at 2500 ppm. Centrilobular hepatocellular vacuolation was increased in incidence in males at 6 and 12 months from 250 ppm, but was not observed in females at these time points or in either sex at 24 months. The most consistent finding was centrilobular hepatocellular hypertrophy, which was observed at all time points in males at 250 ppm and above. Plasma cholesterol was statistically significantly increased in both sexes at 250 ppm and above at 7 months (≥20%) and in males at 12 months (≥52%), and was statistically significantly increased in males at 1000 and 2500 ppm at 18 and 24 months (≥33%), and at 2500 ppm in females at 24 months (63%). Triglyceride levels were also increased (NSS) by 124% and 135% in males and females, respectively, at 2500 ppm.

Table 4. Incidence of non-neoplastic microscopic findings in the liver of rats

Finding	Dose of AE 0317309, dietary concentration in ppm									
	Males					Females				
	0	25	250	1000	2500	0	25	250	1000	2500
6 months										
N examined	9	10	10	10	10	10	10	10	10	10
Hypertrophy, hepatocellular, centrilobular	0	8	10	10	10	0	0	3	4	5
Vacuolation, hepatocellular, centrilobular	1	1	5	3	4	0	0	0	0	0
12 months										
N examined	10	10	9	10	8	9	10	10	9	10
Hypertrophy, hepatocellular, centrilobular	0	0	6	10	6	0	0	0	0	0
Vacuolation, hepatocellular, centrilobular	0	0	2	5	5	0	0	0	0	0
24 months										
N examined	55	55	55	55	55	55	55	54	55	55
Hypertrophy, hepatocellular, centrilobular	0	0	17**	11**	13**	0	0	0	0	1

*p < 0.05.; ** p < 0.01

Pancreas

In the pancreas, diffuse acinar degeneration/atrophy was reported at all time points in treated groups; at 6 months, the incidence of this finding was clearly increased in males and females at 2500 ppm. Only single male animals were recorded with this finding at 12 months at 1000 and 2500 ppm, but the incidence was clearly increased in females at 2500 ppm. At 24 months, there were indications of a dose-response relationship in the incidence of diffuse acinar degeneration/atrophy in both sexes, with statistical significance in males at 1000 and 2500 ppm. Also at 24 months, the incidence of focal acinar degeneration/atrophy was increased in females at 2500 ppm. Other findings included fibrosis, inflammation, and interstitial oedema; however these were generally of a low or sporadic incidence (see table below). It is unlikely that pancreatic histopathology is directly relevant to the hypothesized corneal tumor formation; however, these results have been presented here as support for the adequacy of dosing.

Table 5. Non-neoplastic microscopic findings in the pancreas (number of animals affected)

Findings	Dose of AE 0317309, dietary concentration in ppm									
	Males					Females				
	0	25	250	1000	2500	0	25	250	1000	2500
6 months										
N examined	9	10	10	10	10	10	10	10	9	10
Degeneration / atrophy, acinar, diffuse	0	0	0	0	7	0	0	0	1	8
12 months										
N examined	10	10	9	10	8	9	10	10	9	10
Degeneration / atrophy, acinar, diffuse	0	0	0	1	1	0	0	0	0	7
Fibrosis, interstitial, diffuse	0	0	0	0	5	0	0	0	0	3
Inflammation, acute	0	0	0	1	0	0	0	0	0	5
24 months										
N examined	55	55	54	54	54	55	55	54	55	55
Degeneration / atrophy, acinar, diffuse	0	0	1	8**	9**	0	1	2	4	4
Degeneration / atrophy, acinar, focal	34	34	34	30	30	18	20	25	26	34**
Oedema, interstitial	1	1	0	6	1	0	1	4	6*	2

*p <0.05; ** p < 0.01.

Thyroid

In the thyroid, the incidence of altered colloid was consistently increased in males in all treatment groups. The incidence of increased follicular diameter was increased at 6 and 12 months in males from 250 ppm, but this finding was not observed in males at 24 months or in females at any time point. Pigment deposition in the follicular cells was increased in males at 6 and 12 months from 250 ppm, and at 24 months was statistically significantly increased in both sexes in all treated groups with some suggestion of a dose-response relationship. Focal follicular cell hyperplasia was observed in males at 12 months at 2500 ppm, and at 24 months the incidence was increased above that in control males from 250 ppm. The incidence of diffuse follicular cell hypertrophy was consistently increased in both sexes at 12 and 24 months from 250 ppm.

Table 6. Non-neoplastic microscopic findings in the thyroid (number of animals affected)

Findings	Dose of AE 0317309, dietary concentration in ppm									
	Males					Females				
	0	25	250	1000	2500	0	25	250	1000	2500
6 months										
N examined	9	10	10	10	10	10	10	10	10	10
Altered colloid, basophilic deposits	1	4	8	6	8	0	0	0	0	0
Increased follicular diameter	0	0	1	1	5	0	0	0	0	0
Pigment, brown, follicular cells	0	0	1	1	4	0	0	0	0	0
12 months										
N examined	10	10	9	10	8	9	10	10	9	10
Hyperplasia, follicular cell, focal	0	0	1	0	4	0	0	0	0	0
Hypertrophy, follicular cell, diffuse	0	0	4	5	7	0	0	1	2	1
Altered colloid, basophilic deposits	2	4	8	10	8	0	0	1	1	1
Increased follicular diameter	0	0	5	5	8	0	0	0	0	0
Pigment, brown, follicular cells	1	1	6	8	8	0	0	1	1	0
24 months										
N examined	55	55	54	55	55	55	55	54	55	55
Altered colloid, basophilic deposits	21	24	36**	30	33*	4	3	9	13*	8
Pigment, brown, follicular cells	3	14**	39**	33**	38**	0	7**	14**	14**	18**
Hypertrophy, follicular cell, diffuse	2	2	5	8*	4	0	0	3	7**	2
Hyperplasia, follicular cell, focal	3	2	9	12*	8	0	1	0	1	1

*p<0.05; ** p<0.01

Bayer CropScience sponsored Experimental Pathology Laboratories, Inc. to establish a scientific advisory group consisting of independent consultant pathologists to review several issues involving the thyroid arising from toxicology studies with AE 0317309. The pathology expert group noted that the colloid alterations were present in all groups including controls and that the morphology was similar between control and treated groups; the primary difference being an increase in the number of follicles affected in treated groups. Additionally, colloid changes were seen in the absence of follicular cell hypertrophy, and were not considered to indicate a persistent alteration in thyroid function in this study. Similarly, the brown pigment observed in the follicular cells was considered to be similar in morphology between control and treated animals.

This pigment was evaluated to be suggestive of lipofuscin, which is a normal pigment often associated with aging and seen in a number of organs under untreated conditions. It was the opinion of the pathology expert group that the colloid alteration and pigment deposition observed in rats administered AE 0317309 for two years were representative of normal age-related physiologic changes specific to the rat, and that these findings were not adverse.

Kidney

The incidence of chronic progressive nephropathy (CPN) was slightly increased in males at 6 months at 1000 and 2500 ppm and was clearly increased at 12 months from 250 ppm. At 24 months, chronic progressive nephropathy was common in controls, but the incidence was greater in all treated groups of both sexes, achieving statistical significance in the males. The historical control range for CPN was 27/60-41/60 (45-68%) in males and 16/50-43/60 (32-72%) in females. The incidence of hyperplasia of the collecting ducts was increased in males at 24 months in all treated groups, reaching statistical significance at 1000 and 2500 ppm (see table below). The historical control range for collecting duct hyperplasia was 0/60-9/50 (0-18%) in males and 0/60-6/50 (0-12%) in females.

Table 7. Non-neoplastic microscopic findings in the kidneys (number of animals affected)

Findings	Dose of AE 0317309, dietary concentration in ppm									
	Males					Females				
	0	**25**	**250**	**1000**	**2500**	**0**	**25**	**250**	**1000**	**2500**
6 months										
N examined	9	10	10	10	10	10	10	10	10	10
Nephropathy, progressive, chronic	2	2	2	3	5	0	0	0	0	0
12 months										
N examined	10	10	9	10	8	9	10	10	9	10
Nephropathy, progressive, chronic	3	5	9	10	8	0	0	1	1	0
24 months										
N examined	55	55	55	55	55	55	55	54	55	55
Nephropathy, progressive, chronic	44	51*	54**	52*	51*	37	42	45	45	42
Hyperplasia, collecting ducts	5	11	11	19**	19**	7	9	8	7	5

*p< 0.05; ** p< 0.01

D. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing at the high dose was considered adequate, but not excessive, in male and female Wistar rats. This was based on decreased body weight/body weight gain and non-neoplastic lesions of the eyes, liver, pancreas, thyroid and kidney seen at the high dose. In males, body weight was statistically decreased during the study at 2500 ppm (≤12%). Body weight gains were decreased 7-16%, except late in the study (days 540-708) when body weights declined in all groups including controls. There were also indications of depressed final body weights (≤8%; NSS) and body weight gains (12%) in the female rats at the high dose. Other findings which support that the high dose was adequate include increases in histopathology of the eyes, pancreas, thyroid gland, and kidneys of both sexes which were observed at >25 ppm, as well as increases in centrilobular hepatocellular hypertrophy in males at ≥250 ppm along with minor increases in cholesterol/triglyceride levels. Mortality was increased to 72.7% ($p<0.05$) at 24 months in high-dose males. However, mortality at this dose was similar to that observed at 25 ppm (69.1%; NSS) and, therefore, not considered excessive.

2. Carcinogenicity Study (Mice)

Reference: Steiblen, G. (2006). Carcinogenicity study of AE 0317309 in the C57BL/6 Mouse by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 03172, February 17, 2006. MRID 46801909. Unpublished.

A. Experimental Design

Pyrasulfotole (95.7% w/w a.i.) was administered in the diet to C57BL/6J mice (50/dose) at doses of 0, 100, 1000, or 4000 ppm for males. Groups of 50 females/group received 0, 100, 1000, or 6000 ppm for the first 10 weeks. The high dose in females was reduced to 4000 ppm from week 11 onwards, because it was considered excessive due to increased mortality. The concentrations resulted in doses of 0/0, 13.6/16.7, 137/168, or 560/713 mg/kg/day (M/F) for up to 78 weeks. Additionally, an interim group of 10 mice/sex/dose were treated similarly for up to 52 weeks and then sacrificed.

B. Discussion of Mortality and Tumor Data

Mortality

Both male and female mice showed statistically significant increasing trends for mortality with increasing doses of pyrasulfotole, as well as a significant pair-wise comparison of the 4000 ppm dose group with the controls, all at $p < 0.01$ (Tables 8 and 9) (Memo, L. Brunsman, 3/14/07, TXR No. 0054535). It was stated in the study report that these unscheduled deaths were related to the presence of urinary bladder stones.

Table 8. Male Mouse Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Concentration (ppm)	**1-26**	**27-52**	**53[i]**	**53-81[f]**	**Total**
0	2/60	1/58	9/57	5/48	8/51 (16)**
100	1/60	3/59	9/56	5/47	9/51 (18)
1000	2/59[a]	3/57	10/54	2/44	7/49 (14)
4000	4/60	10/56	9/46	13/37	27/51 (53)**

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.
[f]Final sacrifice at weeks 79-81.

[a]One accidental death at week 20, dose 1000 ppm.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 9. Female Mouse Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks				
Concentration (ppm)	**1-26**	**27-52**	**53[i]**	**53-81[f]**	**Total**
0	3/60	3/57	10/54	9/44	15/50 (30)**
100	0/60	4/60	9/56	5/47	9/51 (18)
1000	2/60	4/58	9/54	3/45	9/51 (18)
4000	14/60	7/46	7/39	12/32	33/53 (62)**

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.
[f]Final sacrifice at weeks 79-81.

( )Percent

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Urinary Bladder Tumors

Male mice had statistically significant trends, and significant pair-wise comparisons of the 4000 ppm dose group with the controls, for urinary bladder transitional cell carcinomas, and papillomas and carcinomas combined, all at $p < 0.01$(Memo, L. Brunsman, 3/14/07, TXR No. 0054535). There was a statistically significant trend for urinary bladder transitional cell papillomas at $p < 0.05$. In addition, although there was only one urethral transitional cell carcinoma at the high dose, there was a statistically significant trend at $p < 0.05$ due to increased mortality at the high dose. In conversations by Lori Brunsman with Dr. John Pletcher, EPA's consulting pathologist, this urethral transitional cell carcinoma should be considered the same tumor type as the transitional cell carcinomas in the urinary bladder. The statistical analyses of the tumors in male mice were based upon Peto's Prevalence Test since there were statistically significant survival disparities among the dose groups (Tables 10 and 11). The historical control incidence for bladder tumors in males was 0/394 across 5 studies (2000-05) performed at Bayer

CropScience Centre de Recherche Sophia Antipolis (CRSA) since the appointment of the current head of pathology.

Table 10. Male Mouse Urinary Bladder Transitional Cell Tumor Rates[+] and Peto's Prevalence Test Results

	Concentration (ppm)			
	0	100	1000	4000
Papillomas (%)	0/46 (0)	0/44 (0)	0/43 (0)	3[a]/33 (9)
p =	0.02155*	-	-	0.06781
Carcinomas (%)	0/47 (0)	0/44 (0)	0/43 (0)	8[b]/34 (24)
p =	0.00000**	-	-	0.00011**
Combined (%)	0/47 (0)	0/44 (0)	0/43 (0)	11/34 (32)
p =	0.00000**	-	-	0.00002**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First papilloma observed at week 71, dose 4000 ppm.
[b]First carcinoma observed at week 69, dose 4000 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 11. Male Urethral Transitional Cell Tumor Rates[+] and Peto's Prevalence Test Results

	Concentration (ppm)			
	0	100	1000	4000
Carcinomas# (%)	0/43 (0)	0/42 (0)	0/42 (0)	1[a]/24 (4)
p =	0.01400*	-	-	0.09036

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

#No adenomas observed.

[a]First carcinoma observed at the final sacrifice at week 79, dose 4000 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Female mice had statistically significant trends for urinary bladder transitional cell papillomas, carcinomas, and papillomas and carcinomas combined, all at $p < 0.01$ (Memo, L. Brunsman, 3/14/07, TXR No. 0054535). There were significant pair-wise comparisons of the 4000 ppm dose group with the controls for urinary bladder transitional cell papillomas and carcinomas, both at $p < 0.05$, and for urinary bladder transitional cell papillomas and carcinomas combined at $p < 0.01$. The statistical analyses of the tumors in female mice were based upon Peto's Prevalence Test since there were statistically significant survival disparities among the dose groups (Table 12). The historical control incidence for bladder tumors in females was 0/380 across 5 studies performed at CRSA.

Table 12. Female Urinary Bladder Transitional Cell Tumor Rates[+] and Peto's Prevalence Test Results

	Concentration (ppm)			
	0	100	1000	4000
Papillomas (%)	0/35 (0)	0/40 (0)	0/42 (0)	2[a]/19 (11)
p =	0.00042**	-	-	0.02632*
Carcinomas (%)	0/35 (0)	0/40 (0)	0/42 (0)	2[b]/19 (11)
p =	0.00042**	-	-	0.02632*
Combined (%)	0/35 (0)	0/40 (0)	0/42 (0)	4/19 (21)
p =	0.00000**	-	-	0.00260**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First papilloma observed at the final sacrifice at week 79, dose 4000 ppm.
[b]First carcinoma observed at the final sacrifice at week 79, dose 4000 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

C. Non-Neoplastic Histopathological Findings

At 18 months, histopathologic findings included a dose-related increase in the incidence of minor to moderate centrilobular hepatocellular hypertrophy in males and females at 1000 and 4000 ppm, which was statistically significant in males at 1000 and 4000 ppm and females at 4000 ppm. Other findings were observed in the urinary system (kidney, urinary bladder, and ureters) at the high dose in males and females, as well as in the prostate in males, and were associated with stones and concretions observed in the urinary system at the same dose (Table 13). Gallstones were observed at an increased incidence in all treatment groups in both sexes. The historical control incidence of gallstones ranged from 0/60-4/60 (0-7%) in males and from 0/60-1/60 (0-2%) in females.

Table 13. Non-neoplastic microscopic findings in all mice at 18 months

Finding	Dose (ppm)							
	Males				Females			
	0	100	1000	4000	0	100	1000	4000
Liver								
N (includes unscheduled and scheduled deaths)	50	50	50	50	50	50	50	50
Centrilobular hepatocellular hypertrophy	0	1	14**	25**	0	0	3	7**
Hepatocellular vacuolation: diffuse	30	26	20	15	37	39	39	23
Hepatocellular vacuolation: mainly periportal: diffuse	0	0	0	7	0	0	0	6
Interstitial mixed cell infiltrate: focal / multifocal	14	19	18	26**	19	20	25	17
Gall bladder								
Gallstones	4	19**	22**	19**	0	5	14**	5**
Epithelial hyperplasia: focal / multifocal	1	2	6	3	0	4	1	3
Kidney								
Pelvic stones: unilateral	0	0	0	10**	0	0	0	21**
Pelvic stones: bilateral	0	0	0	3	0	0	0	3
Collecting ducts hyperplasia: unilateral	0	0	0	7**	2	0	2	13**
Collecting ducts hyperplasia: bilateral	0	0	0	2	0	1	1	0
Pelvic epithelium hyperplasia: unilateral: focal / multifocal	0	0	1	10**	0	0	1	11**
Pelvic epithelium hyperplasia: bilateral: focal / multifocal	0	0	0	1	0	0	1	4**
Papillary fibrosis / atrophy: unilateral	0	0	2	13**	0	0	1	19**
Papillary fibrosis / atrophy: bilateral	0	0	0	12**	0	0	0	4**
Atrophy / fibrosis / scar: cortex / medulla: unilateral	0	0	1	18**	7	10	20**	26**
Atrophy / fibrosis / scar: cortex / medulla: bilateral	0	1	0	21**	1	0	1	9**
Suburothelial mixed cell infiltrate: focal / multifocal	0	0	0	8*	0	0	0	5**
Interstitial hemorrhage(s): focal / multifocal	0	1	0	8**	0	0	0	7
Glomerular chamber dilatation: focal / multifocal	0	0	1	8**	2	3	4	17**
Tubular dilatation: cortex: diffuse	1	3	3	20**	10	4	8	26**
Pelvic dilatation: unilateral	2	1	2	6	2	0	1	12**
Pelvic dilatation: bilateral	0	1	1	33**	1	0	0	15**
Papillary necrosis: unilateral: focal / multifocal	1	0	1	5	0	1	2	4
Papillary necrosis: bilateral: focal / multifocal	0	0	0	2	0	0	0	0

Papillary necrosis: unilateral / bilateral: focal / multifocal	1	0	1	7*	0	1	2	4
Cortical basophilic tubules: unilateral	8	27**	15	14	18	20	13	23*
Collecting duct concretions: unilateral / bilateral	0	0	0	22**	1	3	3	15**
Cyst(s)	5	3	5	7	1	4	3	15**
Medullary tubular mineralization: focal / multifocal	2	1	1	0	0	1	0	6
Arteritis / periarteritis: focal / multifocal	0	0	0	6*	0	0	0	6**
Urinary bladder								
Stones: intraluminal	0	0	0	17**	0	0	0	8**
Stones: intraglandular	0	0	0	2	0	0	0	0
Urothelial hyperplasia: simple: multifocal / diffuse	0	0	1	20**	0	0	0	31**
Urothelial hyperplasia: nodular / glandular: multifocal / diffuse	0	0	0	40**	0	0	0	13**
Urothelial hyperplasia: squamous: multifocal / diffuse	0	0	0	28**	0	0	0	9**
Urothelial hyperplasia: atypical: focal / multifocal	0	0	0	1	0	0	0	2
Distention	11	7	5	37**	4	4	5	19**
Muscular hemorrhage(s) / necrosis: focal / multifocal	0	0	0	5	0	0	0	8
Vascular congestion: focal / multifocal	0	0	0	8*	0	0	0	10*
Interstitial edema: diffuse	0	0	0	42**	0	0	0	27**
Adenomyosis: focal / multifocal	0	0	0	6*	0	0	0	0
Intramuscular inflammatory cell infiltrate: focal / multifocal	3	0	0	27**	1	1	1	20**
Suburothelial mixed cell infiltrate: focal / multifocal	1	0	1	11*	0	0	1	4
Interstitial mixed cell infiltrate: focal / multifocal	0	0	0	17**	0	0	0	8**
Serosal mixed cell infiltrate: focal / multifocal	0	1	1	11**	0	0	0	12**
Prostate								
Intra-urethral stones	0	0	0	3				
Urethral urothelial hyperplasia: simple focal / multifocal	0	0	0	8**				
Adenomyosis: focal / multifocal	0	0	0	3				
Ureters								
Stones	0	0	0	2	0	0	0	0
Urothelial hyperplasia: simple: multifocal / diffuse	0	0	0	3	0	0	0	1

Urothelial hyperplasia: nodular / glandular: multifocal / diffuse	0	0	0	2	0	0	0	2
Dilatation	0	0	1	4	0	0	0	1
Adenomyosis: focal / multifocal	0	0	0	2	0	0	0	0

Data obtained from Tables 10a , b, c, pages 47 -57, and 186 – 247, in the study report.
* $p < 0.05$; ** $p < 0.01$.

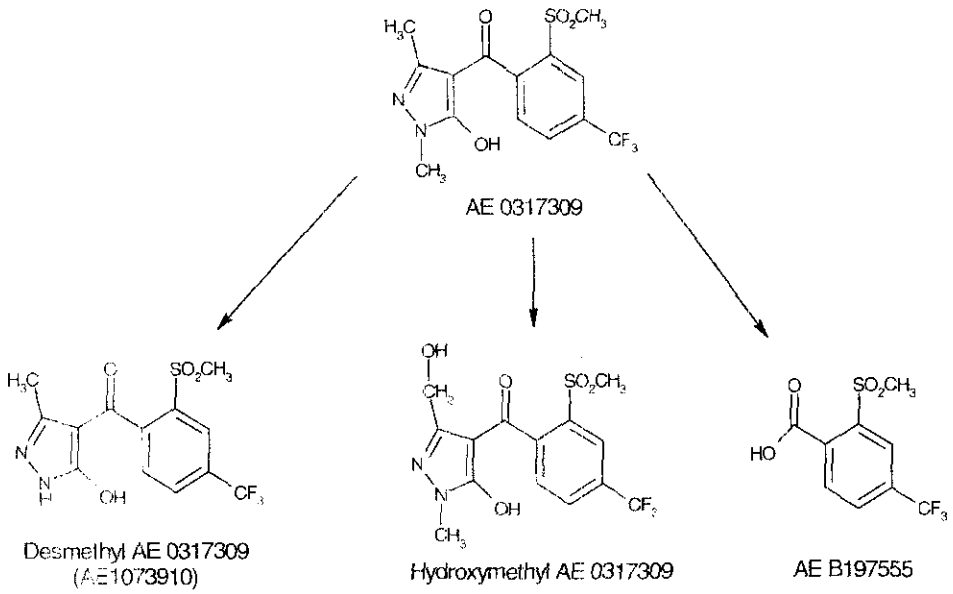
D. Adequacy of Dosing for Assessment of Carcinogenicity

The CARC considered the high dose of 4000 ppm to be excessive in both sexes because of significantly increased mortality in males (53% vs 16% in controls) and females (62% vs 30% in controls), much of which occurred in the first year of the study. The increased mortality was due to the presence of urinary bladder stones. The CARC could not dismiss these rare bladder tumors, but their relevance to human risk was lessened because these tumors were seen only at the dose where death, stones, and bladder hyperplasia were evident. In addition, dose selection for the long term study was reasonable based on the results of the 90-day mouse study where no effects were seen at 3000 ppm.

IV. TOXICOLOGY

1. Metabolism

In a disposition study in male rats (MRID 46801918) in which single doses of pyrasulfotole (10 mg/kg bw) were administered orally, 100% of the dose was recovered in 52 hours, with 70% of the dose being excreted in urine and 30% in feces. Less than 2% of the administered dose remained in residual carcass and tissues after 52 hours. Hydroxymethyl AE 0317309 (2%), desmethyl AE 0317309 (<9%), and AE B197555 (benzoic acid; <2%) were observed as metabolites in urine and feces; further metabolism of pyrasulfotole is unknown. Metabolic transformations are depicted below:



2. Mutagenicity

An assessment of the mutagenicity of the **parent compound**, pyrasulfotole, was based on the following four acceptable/guideline genetic toxicology studies:

1. In an in vitro reverse gene mutation test with *Salmonella typhimurium* strains TA1535, TA100, TA1537, TA98 and TA102 at concentrations up to 5000 µg/plate (limit concentration), pyrasulfotole was not mutagenic with or without metabolic activation (MRID 46801911).

2. In an in vitro mammalian cell gene mutation assay in Chinese hamster V79 cells at the HGPRT locus at concentrations up to 960 µg/mL (pH of culture medium changed above 312.5 µg/mL in prelim. cytotox. test), pyrasulfotole was not mutagenic with or without metabolic activation (MRID 46801912).

3. In an in vitro mammalian cell cytogenetics assay with Chinese hamster V79 cells at concentrations up to 2500 µg/ml (cytotoxic) in the presence and absence of metabolic activation, there was no evidence of clastogenicity induced above background at non-cytotoxic concentrations (MRID 46801913).

4. In an in vivo micronucelus assay performed in NMRI mice, no increase in micronuclei was seen following i.p. dosing up to and including 500/1000 mg/kg bw (M/F) (MRID 46801914). Mortality was observed in a pilot study above 500 mg/kg bw; 8/10 females died at 1000 mg/kg bw in the main study.

An assessment of the mutagenicity of the **benzoic acid metabolite** (AE B197555; RPA 203328) of pyrasulfotole was also conducted using the following four

acceptable/guideline genetic toxicology studies:

1. In an in vitro reverse gene mutation test with *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 at concentrations up to 5000 µg/plate (limit concentration), pyrasulfotole was not mutagenic with or without metabolic activation (MRID 43904814).

2. In an in vitro mammalian cell gene mutation assay in Chinese hamster ovary cells at the HGPRT locus at concentrations up to 2700 µg/mL (cytotoxic), pyrasulfotole was not mutagenic with or without metabolic activation (MRID 44545303).

3. In an in vitro mammalian cell cytogenetics assay with Chinese hamster ovary cells at concentrations up to 2710 µg/ml (~10 mM) in the presence and absence of metabolic activation, there was no evidence of clastogenicity induced above background (MRID 44545301).

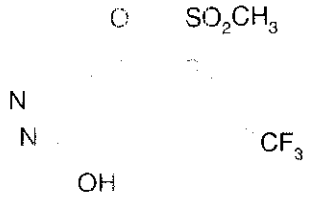
4. In an in vivo micronucelus assay performed in Crl:CD-1®(ICR)BR mice, no increase in micronuclei was seen following oral dosing up to and including 2000 mg/kg bw (limit dose) (MRID 44545302).

Based on the overall findings, the parent compound, pyrasulfotole or its benzoic acid metabolite, AE B197555, do not pose a mutagenic concern.

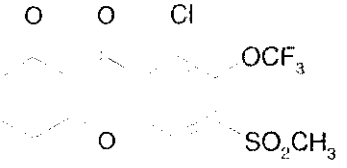
3. Structure-Activity Relationships

Pyrasulfotole and a variety of other structurally related herbicides (*tembotrione, mesotrione,* NTBC, *topramezone, isoxaflutole*) are capable of inhibiting HPPD to various degree. With the exception of isoxaflutole (which does not contain a hydroxy group on the 5-membered ring), all these herbicides either contain a beta-diketo structural moiety or can be converted to a beta-diketo moiety via keto-enol tautomerization.

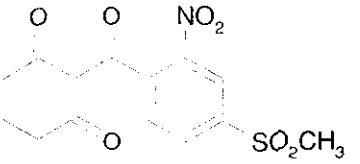
Pyrasulfotole

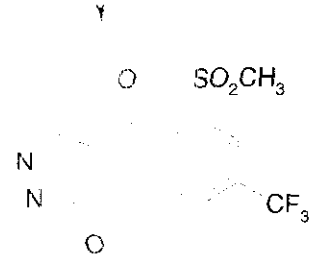


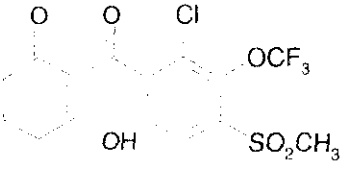
Tembotrione



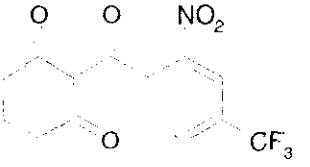
Mesotrione



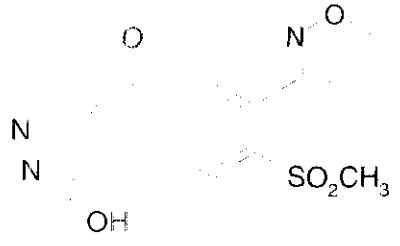




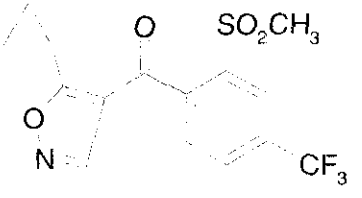
NTBC



Topramezone (BAS 670 H)



Isoxaflutole



Both pyrasulfotole and tembotrione have been shown to induce rare corneal tumors in male rats but not in female rats or mice. NTBC has been shown to induce corneal lesions in male rats and beagle dogs but not in mice, rabbits and monkeys (Lock et al., 2006). Mesotrione was classified by HIARC in 2001 as "not likely to be carcinogenic to humans" by all route of exposure based upon lack of evidence of carcinogenicity in rats and mice. Topramezone was classified by CARC in 2005 as "not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis" based on treatment-related increases in thyroid follicular cell tumors in male and female rats. There was some evidence of corneal hyperplasia but no tumors. In 1996, isoxaflutole was classified as "likely to be a human carcinogen" based on increases in liver tumors in both sexes of mice and rats and increases in thyroid follicular cell tumors in male rats. There was no significant concern for mutagenicity for any of these herbicides.

4. Chronic and Subchronic Toxicity

a) Chronic Toxicity

Combined Chronic Toxicity/Carcinogenicity – Rat

Reference: Wason S. (2006). 6-Month toxicity, chronic toxicity and carcinogenicity study of AE 0317309 in the Wistar rat by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 02453, February 28, 2006. MRID 46801910. Unpublished.

In a combined chronic toxicity/carcinogenicity study (MRID 46801910), AE 0317309 (95.7% a.i., batch Op. 1-4) was administered in the diet to 75 six-week-old Wistar Rj:WI (IOPS HAN) rats/sex/group at dose levels of 0, 25, 250, 1000, or 2500 ppm (equivalent to 0/0, 1.0/1.4, 10/14, 41/57, or 104/140 mg/kg bw/day in males/females) for 24 months. Animals were sacrificed at 6 (10/dose group), 12 (10/dose group), and 24 months (55/dose group).

There were no treatment-related effects on food consumption and hematology. Mortality was 73% ($P<0.05$) in high-dose males at 24 months; however, survival was >25% after 24 months in control and all treated groups and therefore was considered acceptable for evaluating the carcinogenic potential of pyrasulfotole. Increased incidences of white area on the eye and soiled fur in one or more areas were observed clinically in males and females at all time points at ≥250 ppm. Body weight in males was decreased (≥10%) throughout the study at ≥1000 ppm. A consistent treatment-related effect on body weight or body weight gain was not observed in treated females. During ophthalmoscopic examination, corneal opacity, neovascularization of the cornea, edema of the cornea, and "snow flake" corneal opacities were observed in males at ≥250 ppm after 6, 12, and 24 months of treatment. Similar effects were observed in females during treatment at ≥250 ppm. Plasma cholesterol was increased in males and females at 250 ppm at 7 months (≥20%) and in males at 12 months (≥52%). Plasma cholesterol was also increased in males at ≥1000 ppm at 18 and 24 months (≥33%) and at 2500 ppm in females at 24 months (63%). Increases in cholesterol at ≥250 ppm were considered toxicologically significant in light of the increased incidence of hepatocellular hypertrophy and/or vacuolation and increased liver weight throughout the study. Triglyceride levels were also increased (NSS) by 124% and 135% in males and females, respectively, at 2500 ppm. Increased levels of ketones were observed in the urine of males and females at ≥1000 ppm at all collection periods and in males at 250 ppm at months 19 and 24 only. Urinary pH was decreased at ≥250 ppm in males at all time points and in females at 3 months only. Urinary protein was increased in males in all treatment groups from 6 months onwards. Decreases in urinary pH and increased urinary protein at ≥250 ppm in males were considered toxicologically significant in conjunction with treatment-related increases in collecting duct hyperplasia at these same doses. The increased level of ketones may have been due to unmetabolized test substance. Since chronic progressive nephropathy is specific to the rodent, increased incidences in treated animals were not considered relevant for human risk assessment.

Absolute and relative liver and kidney weights were elevated in males at ≥250 ppm from 6 months onwards (liver: 20%; kidney: >15%). There were no significant effects on organ weights in females. At macroscopic examination, the incidence of eye opacities was increased in males and females at ≥250 ppm. Enlarged liver was observed in males at 6 months in all treated groups and at 12 months at ≥250 ppm. At 24 months, there was an increased incidence among males of pale kidneys and irregular surface of the kidney at ≥1000 ppm. Non-neoplastic histopathology is summarized above.

Carcinogenicity – Mouse

Reference: Steiblen, G. (2006) Carcinogenicity study of AE 0317309 in the C57BL/6 Mouse by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 03172. February 17, 2006. MRID 46801909. Unpublished.

In a carcinogenicity study (MRID 46801909), AE 0317309 (95.7% w/w a.i.) (95.7% w/w a.i.; Batch No. OP. 1-4) was administered in the diet to C57BL/6J mice (50/dose) at doses of 0, 100, 1000, or 4000 ppm for males. Groups of 50 females/group received 0, 100, 1000, or 6000 ppm for the first 10 weeks, then reduced the high-dose to 4000 ppm from week 11 onwards. The high-dose in females was considered excessive because of increased mortality. The concentrations resulted in doses of 0/0, 13.6/16.7, 137/168 and 560/713 mg/kg/day in males and females for up to 78 weeks. Additionally, 10 mice/sex/dose were treated similarly for up to 52 weeks and then scheduled for interim sacrifice.

At 4000 ppm, survival at 18 months was 50 and 40%, respectively in males and females. Survival is above the guideline recommended level and is acceptable. Survival at 100 and 1000 ppm were comparable to controls. At 4000 ppm clinical signs include hardness in the urinary bladder area, soiled fur, reduced motor activity, labored or rapid respiration and red urine. The study authors presumed red urine color was due to compound excretion, however, no urine analysis was performed to confirm. At 4000 ppm mean body weight was significantly decreased in both males and females. Body weight was unaffected at 1000 ppm in males and females. Red blood cells, Hb, Hct, and MCHC were decreased in females at 4000 ppm at 18 months (showing indications of dose-response relationships). MCV was slightly increased in females at 4000 ppm at 18 months. In males at 4000 ppm, similar hematological effects were generally observed at 18 months. The perturbations seen at 4000 ppm were considered to be treatment-related. Hematological changes at 1000 ppm were comparable to controls.

The majority of statistically significant organ weight changes were restricted to 4000 ppm mice sacrificed at 18 months. Absolute and relative kidney weights increased in males and males at 4000 ppm dose group at the terminal sacrifice. Absolute brain weight was reduced at 4000 ppm at 18 months in males, although it was actually significantly increased as a percentage of body weight. Relative liver weights were increased in both males and females at 18 months, reaching statistical significance in all treated males, with no clear dose-response associated effects on absolute liver weights. Absolute and relative spleen weights were increased in males and relative

spleen weights in females at 18 months in 4000 ppm group.

In all treatment groups (males and females) at 12 months, incidences (n= 7 - 10) of the following macroscopic observations were increased in the kidneys: (i) large kidneys (2-7 treated vs 0 control); (ii) small kidneys (1-4 treated vs 0 controls); stones (1-4 vs 0 control); pelvic dilation (3-6 vs 0 control); pale (1-3 vs 0 control) cysts (1-2 vs 0 control) gritty content in the bladder (6-8 vs 0 control) and distended bladder (4-8 vs 0 control). At 18 months, the majority of those which died unscheduled at 4000 ppm were found to have died due to acute or chronic renal failure, due to urinary tract blockage or chronic kidney and/or urinary bladder inflammation, respectively. Stones were found in the kidney and/or urinary bladder of these animals; other findings at necropsy of unscheduled deaths were enlarged or small kidneys, renal pelvic dilation, pale kidneys, renal cyst(s), distention of the urinary bladder, and gallbladder stones or concretions. Similar findings were observed in animals sacrificed at 18 months. The incidences of the above findings at 4000 ppm were higher than the incidence at 12 months of sacrifice.

Increased incidence of gallstones was a relatively common macroscopic observation in all treated groups at scheduled sacrifice, although there was no dose-response relationship. Non-neoplastic histopathology is summarized above.

b) Subchronic Toxicity

90-day oral (rat)

Reference: Langrand-Lerche, C. (2003). AE0317309 90-day toxicity study in the rat by dietary administration. Bayer CropScience 355, rue Dostoievski, BP 153, F-06903 Sophia Antipolis Cedex , Laboratory Study No.: SA02017, July 30, 2005. MRID 46801842. Unpublished.

In a 90-day oral toxicity study (MRID 46801842), AE 0317309 (97.4% w/w a.i., batch H2235) was administered in the diet to groups of 10 Rj:WI(IOPS HAN) Wistar rats rats/sex/dose at dose levels of 0, 2, 30, 1000, 7000 and 12000 ppm (equivalent to 0.0, 0.13, 1.96, 66, 454, and 830 mg/kg bw/day for males and 0.0, 0.15, 2.32, 77, 537 and 956 mg/kg bw/day in females) for a period of 90 days.

No abnormalities were detected during the neurotoxicity assessment and there were no treatment related effects on hematological parameters. At 12000 ppm, six male and one female were either sacrificed for humane reasons or were found dead during the treatment period. The group was terminated at week 11 due to excessive toxicity. At 7000 ppm, two males were found dead or were sacrificed for humane reasons during the treatment period. Treatment related clinical signs were observed in a large number of rats at 7000 and 12000 ppm and consisted of intensely yellow colored urine associated on a few occasions with soiled anogenital area, soiled fur, piloerection, general pallor and wasted appearance. Other clinical signs noted included: few or no feces, cold to touch, reduced motor activity, labored respiration, hunched posture, increased salivation and

soiling around the mouth. White areas on eyes were noted in two males at 7000 ppm and in one male and four females at 12000 ppm. At 1000 ppm, yellow colored urine was noted in all males on a few days and one female presented a white area on the eyes.

At 12000 ppm, a reduction in mean body weight gain of 70% was recorded in males during the first week of exposure. At this dose level, the depressions in body weight gain ranged from 11.5 to 56% over days 22 to 70. In females at 7000 ppm and 12000 ppm, the depressions in mean body weight gain were 12.5 and 15.6%, respectively, relative to controls at the end of the 90 day period. At 12000 ppm food consumption in males was lower than control values throughout the study. In females at 12000, the mean food consumption was lower than control value on the first week of treatment only (reduction of 28%) without reaching statistical significance. At 7000 ppm, a reduction of food consumption was noted during the first week in males (28%) and females (15%), the difference with controls reaching statistical significance in males only. Very slight reductions thereafter were also observed in both sexes but were not statistically significant.

Neovascularization of the cornea and characteristic "snowflake" corneal opacities were noted at 7000 and 12000 ppm in males, and at 1000, 7000, and 12000 ppm in females. In males, bilirubin, AST and ALT, urea, and creatinine were increased (but not statistically significantly) at 7000 ppm. Cholesterol was statistically significantly ($p \leq 0.01$) increased in males at 1000 ppm (45%) and 7000 ppm (51%). Triglycerides were statistically significantly ($p \leq 0.01$) increased in males at 1000 ppm (112%) and 7000 ppm (68%). Ketone levels were increased from 1000 ppm in both males and females. This is likely due to detection of the diketone structure of the test substance itself, as the vast majority of the parent molecule is excreted in the urine unchanged. There was an increased incidence of occult blood, erythrocytes, leukocytes, and epithelial cells in the urine in both males and females at 7000 ppm and in females at 12000 ppm (males in the 12000 ppm group did not survive until the end of the study and urine was therefore not collected).

At 1000 ppm and 7000 ppm, the relative liver to body weight in males was statistically significantly increased by 22 and 26% respectively. At 1000 ppm and 7000 ppm, relative kidney to body weight in males was increased 3.5 and 38.6%, respectively, the latter increase being statistically significant. For females relative liver weight was increased 8.7, 13 and 8.7% at 1000, 7000 and 12000 ppm and relative kidney weight was increased 8, 25.4 and 30%, respectively.

At 7000 ppm and 12000 ppm, abnormal shape of the kidneys, mottled kidneys, dilation of and gritty content in the renal pelvis, gritty content, distension of the urinary bladder, and gritty content of the ureters, and enlarged livers were observed in males and females. Livers were enlarged in 3/10 males at 1000 ppm. Prominent lobulation was noted in 1/7 male at 7000 ppm and in 2/10 males at 1000 ppm. The thyroid gland was enlarged in one male at 1000 ppm.

The 12000 ppm group was terminated early at 11 weeks and tissues from animals in this group were not microscopically examined. **Histological changes associated with the presence of calculi (urolithiasis) were found in the kidneys/urinary bladder/ureters in 4/8 males and 6/10 females at 7000ppm. Associated histological changes included: pelvic dilatation (unilateral or bilateral), urinary epithelial hyperplasia (pelvis, urinary bladder and ureters), interstitial fibrosis of the urinary tract, cystitis and ureteritis.** Slight to moderate diffuse centrilobular hepatocellular hypertrophy was observed in 6/7 males at 7000 ppm, in 9/10 males at 1000 ppm and in 1/10 female at 7000 ppm. In females, a periportal vacuolation was found in 8/10 animals at 7000 ppm and 3/10 animals at 1000 ppm.

28-day oral (mouse)

Reference: McElligott, A. (2002). AE 0317309: Preliminary 28-day toxicity study in the mouse by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 02080. September 17, 2002. MRID 46801843. Unpublished.

In a 28-day oral toxicity study (MRID 46801843), Pyrasulfotole (97.4% w/w a.i., batch H2235) was administered to 10 C57BL/6J mice/sex/dose in the diet at dose levels of 0, 200, 1000, or 5000 ppm (equal to 0/0, 35.8/45.0, 192/233, or 961/1082 mg/kg bw/day in males/females). There were no compound-related effects on mortality, clinical signs, body weight, food consumption, clinical chemistry, or organ weights. **Gritty content was found in the urinary bladder of 2/10 males at 5000 ppm. This finding was considered to be treatment-related, since analyses of gritty urinary tract content or urinary tract stones found in other studies (90-day rat toxicity study, mouse carcinogenicity study) have shown that the urinary tract material contains a high concentration of test substance.** Pale livers were noted in 5/10 females at 5000 ppm. Spleens with a black focus were observed in 4/10 females at 5000 ppm (vs. 1/10, 2/10, and 2/10 females at 0, 200, and 1000 ppm, respectively). In the absence of histopathology in the spleen, this effect was not considered toxicologically significant. **In 3/10 males at 5000 ppm, examination of the urinary bladder revealed diffuse urothelial hyperplasia, diffuse submucosal granulation tissue, and diffuse suburothelial mixed-cell infiltrate. Urinary calculi were also observed in one of these 3 males at 5000 ppm.**

Multifocal, centrilobular hepatocytic microvacuolation was observed in the livers of 8/10 and 9/10 males at 1000 and 5000 ppm, respectively (vs. 5/10 and 6/10 males at 0 and 10 ppm, respectively). Multifocal, centrilobular hepatocytic microvacuolation was also observed in 5/10 females at 5000 ppm (vs. 3/10, 4/10, and 4/10 females at 0, 200, and 1000 ppm, respectively). Hepatocytic microvacuolation was not considered toxicologically significant in the absence of other evidence of hepatotoxicity and since it was not observed at any dose in the 90-day toxicity study in the rat. Focal/multifocal subcapsular hyperplasia of the adrenal glands was observed in 6/10 females at 5000 ppm (vs. 3/10, 0/10, and 0/10 females at 0, 200, and 1000 ppm, respectively). Because linear dose response was lacking for this observation and statistical analysis was not performed, the finding was considered a high-dose effect. **The results of this study were not replicated in the 90-day toxicity study in the mouse; however, this may have**

been due to dose spacing.

90-day oral (mouse)

Reference: Steiblen, G. (2003). AE 0317309: 90-day toxicity study in the mouse by dietary administration. Bayer CropScience, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 03015, November 21, 2003. MRID 46801844. Unpublished.

In a 90-day oral toxicity study (MRID 46801844), pyrasulfotole (95.7% w/w a.i., batch Op. 1-4) was administered to 10 C57BL/6 J@ Ico mice/sex/dose in the diet at dose levels of 0, 100, 1500, or 3000 ppm (equal to 0/0, 16.5/19.7, 124/152, 259/326, or 500/617 mg/kg bw/day for males/females). There were no compound-related effects on mortality, clinical signs, ophthalmology, body weight, food consumption, clinical chemistry, organ weights, or gross and histologic pathology. **Urinary pH was slightly increased at 3000 ppm in females (6.3, $p<0.05$ vs. 6.0 in controls).** Due to the small number or volume of samples obtained, urinary pH was not measured in 3000 ppm males. Examination of the individual animal data revealed that urinary pH for the other male dose groups was similar to controls (~6.0).

5. Modes of Action

***Corneal tumors* (male rat):** In the study reports for the cancer studies in rats and mice, it was stated that corneal tumors were the result of a nongenotoxic mode of action that was secondary to corneal inflammation and regenerative hyperplasia caused by tyrosine; however, a mode of action analysis was not submitted to support this conclusion. A search of the National Center for Biotechnology Information (NCBI) biomedical literature database, PubMed, did not yield any information supporting an association between tyrosinemia and ocular tumors in rodents or humans. The following table lists putative key precursor events to ocular tumor formation in males that were observed in two toxicology studies in rats:

Table 14. Putative key events in male rat corneal carcinogenesis

Route of Exposure and Duration	Key Responses	Concentration (Dose)
Oral (diet): 24 months	Corneal inflammation/corneal neovascularization	250 (10 mg/kg/day), 1000 (41 mg/kg/day), and 2500 ppm (104 mg/kg/day) (6, 12, and 24 months)
	Corneal regenerative hyperplasia	250 (10 mg/kg/day), 1000 (41 mg/kg/day), and 2500 ppm (104 mg/kg/day) (6, 12, and 24 months)
	Squamous cell papilloma/carcinoma	2500 ppm (104 mg/kg/day) [M] only
Oral (diet): 90 days	Snowflake corneal opacities/corneal neovascularization	7000 (454 mg/kg/day) and 12000 ppm (830 mg/kg/day)

Bladder tumors (mouse): These tumors were considered by the registrant to be the result of a non-genotoxic proliferative mechanism due to the concurrent presence of secondary inflammation and hyperplastic findings in the urinary bladder, induced by the urinary stones. A mode of action analysis was not submitted to support this conclusion; however, as the following table demonstrates, dose and temporal concordance among putative key events were observed in two mouse toxicology studies. In addition, it is noted that in the carcinogenicity study in mice, bladder tumors were observed only at that dose at which urinary bladder stones or concretions were also observed.

Table 15. Putative key events in male and female mouse urinary bladder carcinogenesis

Route of Exposure and Duration	Key Responses	Concentration (Dose)
Oral (diet): 78 weeks	Urinary stones; Inflammatory cell infiltrate (intramuscular); Urothelial hyperplasia; Transitional cell papillomas/carcinomas	4000 ppm (560/713 [M/F] mg/kg/day) only
Oral (diet): 28 days	Gritty content/urinary calculi; Suburothelial mixed-cell infiltrate; Urothelial hyperplasia	5000 ppm (961/1082 [M/F] mg/kg/day) only
Oral (diet): 90 days	--No effects seen.--	≤3000 ppm (500/617 [M/F] mg/kg/day)

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

The CARC concluded the following:

1. Carcinogenicity

Rats

- There were no treatment-related increases in tumors in female Wistar rats.

- An increased incidence of corneal tumors (squamous cell papilloma and carcinoma) was observed in males at the high dose (2500 ppm) only. The incidences of these rare tumors observed in two males were not analyzed statistically, since they were so low individually (1/55 each, 2500 ppm vs 0/55, control) and when combined (2/55, 2500 ppm vs 0/55, control). However, the incidence did exceed the historical control incidence of these tumors (0/403 in males) in 7 studies conducted from 2000-2005 at Bayer CropScience Centre de Recherche Sophia Antipolis. In addition, corneal hyperplasia, a preneoplastic lesion, was seen at the high dose. **Therefore, the CARC concluded that these rare corneal tumors were treatment-related.**

- Adequacy of Dosing: Dosing at the high dose was considered adequate, but not excessive, in male and female Wistar rats. This was based on decreased body weight/body weight gain and non-neoplastic lesions of the eyes, liver, pancreas, thyroid and kidney seen at the high dose. In males, body weight in males was statistically decreased during the study at 2500 ppm (≤12%). Body weight gains were decreased 7-16%, except late in the study (days 540-708) when body weights declined in all groups including controls. There were also indications of depressed final body weights (≤8%; NSS) and body weight gains (12%) in the female rats at the high dose.

Other findings which support that the high dose was adequate include increases in histopathology of the eyes, pancreas, thyroid gland, and kidneys of both sexes which were observed at >25 ppm, as well as increases in centrilobular hepatocellular hypertrophy in males at ≥250 ppm along with minor increases in cholesterol/triglyceride levels. Mortality was increased to 72.7% ($p<0.05$) at 24 months in high-dose males. However, mortality at this dose was similar to that observed at 25 ppm (69.1%; NSS) and, therefore, not considered excessive.

Mice

- Male C57BL/6 mice had statistically significant trends, and significant pair-wise comparisons of the 4000 ppm dose group with the controls, for urinary bladder transitional cell carcinomas (8/34 (24%) vs 0/47, controls), and papillomas and carcinomas combined (11/34 (32%) vs 0/47, controls), all at $p < 0.01$. There was also a statistically significant trend for urinary bladder transitional cell papillomas at $p < 0.05$. In addition, although there was only one urethral transitional cell carcinoma at the high dose (1/24 (4%)), there was a statistically significant trend at $p < 0.05$ due to increased mortality at the high dose. This urethral transitional cell carcinoma should be considered the same tumor type as the transitional cell carcinomas in the urinary bladder. No tumors were seen at 100 or 1000 ppm. The incidence of tumors at the high dose exceeded the historical control data for bladder tumors in males (0/394) across 5 studies (2000-2005) performed at Bayer CropScience Centre de Recherche Sophia Antipoli (CRSA). **Therefore, the CARC considered these tumors at the high dose to be treatment related.**

- Female mice had statistically significant trends for urinary bladder transitional cell papillomas, carcinomas, and papillomas and carcinomas combined, all at $p < 0.01$. There were significant pair-wise comparisons of the 4000 ppm dose group with the controls for both urinary bladder transitional cell papillomas (2/19 (11%) vs 0/35, controls) and carcinomas (2/19 (11%) vs 0/35, controls), both at $p < 0.05$, and for urinary bladder transitional cell papillomas and carcinomas combined (4/19 (21%)) vs 0/35, control) at $p < 0.01$. The incidence of the tumors at the high dose exceeded the historical control incidence for bladder tumors in females (0/380 across 5 studies performed at CRSA). **Therefore, the CARC considered these tumors at the high dose to be treatment related.**

- Adequacy of Dosing: The CARC considered the high dose of 4000 ppm to be excessive in both sexes because of significantly increased mortality in males (53% vs 16% in controls) and females (62% vs 30% in controls), much of which occurred in the first year of the study. The increased mortality was due to the presence of urinary bladder stones. The CARC could not dismiss these rare bladder tumors, but their relevance to human risk was lessened because these tumors were seen only at the dose where death, stones, and bladder hyperplasia were evident. In addition, dose selection for the long term study was reasonable based on the results of the 90-day mouse study where no effects were seen at 3000 ppm.

2. Mutagenicity

The parent compound, pyrasulfotole and its benzoic metabolite, AE B197555, do not pose a mutagenic concern.

3. Structure Activity Relationship

Pyrasulfotole and a variety of other structurally related herbicides (tembotrione, mesotrione, NTBC, topramezone, isoxaflutole) are capable of inhibiting HPPD to various degrees. With the exception of isoxaflutole (which does not contain a hydroxy group on the 5-membered ring), all these herbicides either contain a beta-diketo structural moiety or can be converted to a beta-diketo moiety via keto-enol tautomerization. Both pyrasulfotole and tembotrione have been shown to induce rare corneal tumors in male rats but not in female rats or mice. NTBC has been shown to induce corneal lesions in male rats and beagle dogs but not in mice, rabbits and monkeys. Mesotrione was classified by HIARC in 2001 as "not likely to be carcinogenic to humans" by all route of exposure based upon lack of evidence of carcinogenicity in rats and mice. Topramezone was classified by CARC in 2005 as "not likely to be carcinogenic to humans at doses that do not alter rat thyroid hormone homeostasis" based on treatment-related increases in thyroid follicular cell tumors in male and female rats. There was some evidence of corneal hyperplasia but no tumors. In 1996, isoxaflutole was classified as "likely to be a human carcinogen" based on increases in liver tumors in both sexes of mice and rats and increases in thyroid follicular cell tumors in male rats. There was no significant concern for mutagenicity for any of these herbicides.

4. Mode of Action

Corneal Tumors (male rat): While the CARC considered it was biologically plausible for corneal tumors to result from a nongenotoxic mode of action that was secondary to corneal inflammation and regenerative hyperplasia caused by tyrosine, inadequate data were available to firmly support this mode of action.

Bladder tumors (mice): While the CARC considered that it was biologically plausible for the bladder tumors in male and female mice to be the result of a non-genotoxic proliferative mechanism due to the concurrent presence of secondary inflammation and hyperplastic findings in the urinary bladder, induced by the urinary stones, inadequate data were available to firmly support this mode of action. However, it is noted that there was dose and temporal concordance among putative key events that were observed in two mouse toxicology studies. In addition, in the carcinogenicity study in mice, bladder tumors were observed only at that dose at which urinary bladder stones or concretions were also observed.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified pyrasulfotole as "Suggestive Evidence of Carcinogenic Potential". This was based on the following weight of evidence considerations:

1. Two male rats had rare treatment-related corneal tumors at the highest dose tested (2500 ppm [104/140 mg/kg/day, M/F]), which was a dose associated with widespread corneal inflammation, hyperplasia, metaplasia, neurovascularization and atrophy.
2. Treatment-related urinary bladder transitional cell tumors were seen in male and female mice only at the highest dose tested (4000 ppm [560/713 mg/kg/day, M/F]). The highest dose tested in mice was considered to be excessive due to increased mortality caused by the presence of urinary bladder stones. The fact that these tumors were seen only in the presence of increased mortality, along with hyperplasia and stone formation, lessens their relevance for human risk.
3. While the CARC noted the progression of non-neoplastic related lesions in both the rats and mice and acknowledged biologically plausible non-genotoxic modes of action for both the corneal tumors and the bladder tumors, they concluded that there was insufficient data at this time to fully support the modes of action.
4. There is no mutagenicity concern for pyrasulfotole.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Quantification of carcinogenic potential is not required. The chronic Reference Dose (cRfD) of 0.01 mg/kg/day, derived from the NOAEL of 1.0 mg/kg/day in rats along with an uncertainty factor of 100, would be protective of both non-cancer and cancer effects.

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IX. Appendix: Photomicrographs of corneal tumors[1]

Figure 1. Microphotograph (25x magnification) of the corneal squamous cell carcinoma observed at 2500 ppm in the rat study conducted with AE 0317309.

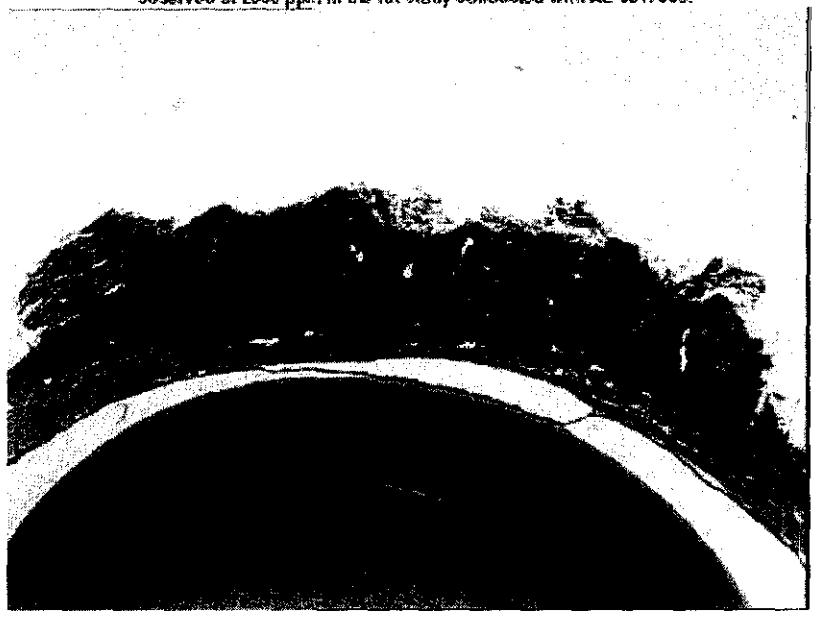
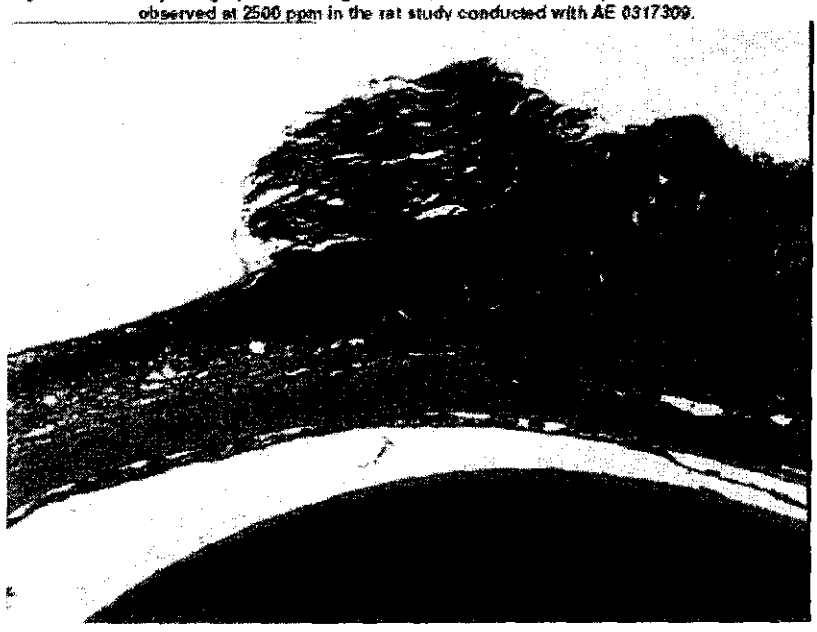


Figure 2. Microphotograph (50x magnification) of the corneal squamous cell carcinoma observed at 2500 ppm in the rat study conducted with AE 0317309.



1 Extracted from Bayer CropScience document, "Historical control data for selected findings from the rat chronic/oncogenicity study SA 02453"; no MRID

Figure 3. Microphotograph (100x magnification) of the corneal squamous cell carcinoma observed at 2500 ppm in the rat study conducted with AE 0317309.

Figure 4. Microphotograph (50x magnification) of the corneal squamous cell papilloma observed at 2500 ppm in the rat study conducted with AE 0317309.

Figure 5. **Microphotograph (100x magnification) of the corneal squamous cell papilloma observed at 2500 ppm in the rat study conducted with AE 0317309.**