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

JUL 23 1992

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Propargite

FROM: John Doherty, Ph.D. John Doherty 5/14/92
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

and
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Science Analysis and Coordination Branch
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TO: George LaRocca
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Reregistration Division (H7505C)

and
Lois Rossi
Product Manager #74
Special Review and Reregistration Division (H7508C)

The Health Effects Division Carcinogenicity Peer Review Committee met on February 12, 1992 to discuss and evaluate the weight-of-the-evidence on propargite with particular reference to its carcinogenic potential. The Peer Review Committee agreed that propargite should be classified as Group B2- probable human carcinogen- based on evidence for induction of sarcomas in the jejunum of rats.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Penelope Fenner-Crisp Penelope A. Fenner-Crisp

William L. Burnam

Reto Engler

Karl Baetcke

Lucas Brennecke

Marion Copley

Kerry Dearfield

George Ghali

Hugh Pettigrew

Jean Parker

Esther Rinde

Yin-Tak Woo

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

John Doherty[1]

Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Julie Du

Marcia Van Gemert

Robert Beliles

Richard Hill

William Sette

John Quest

4. Other Attendees: (Observers)

Eve Andersen (Clement), Kris Khanna (ODW), Lori Brunsman (HED), Lawrence Chitlick (HED)

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[1] Also a member of the committee for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

B. Material Reviewed:

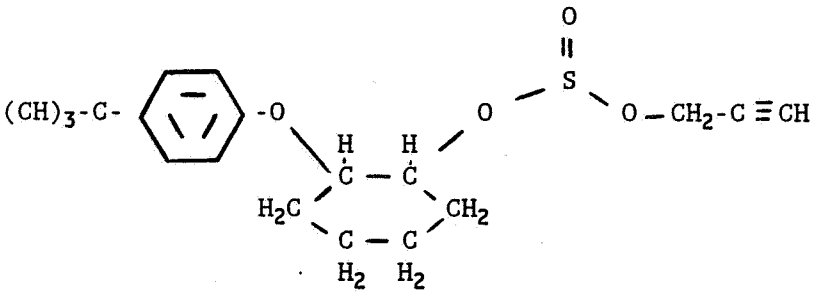
The material available for review consisted of DER's, data on metabolism, one-liners, and other data summaries prepared by John Doherty; tables and statistical analysis by Bernice Fisher. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by Uniroyal Chemical Co.

C. Background Information:

Propargite [butyl(phenoxy)cyclohexyl-2-propynyl sulfite], also called Omite, is a broad spectrum acaricide. There are tolerances (listed under 180.259) for many raw agricultural commodities including fruits, nuts, meat and meat byproducts, eggs, potatoes, grains and peanuts. Propargite was the subject of a 1986 Registration Standard.

The Caswell (or Tox Chem) Number of propargite is 130I.
The Chemical Abstracts Registry Number (CAS No.) is 2312-35-8.
The PC Number is 097601.

The structure of propargite is



D. Evaluation of Carcinogenicity Evidence:

1. Sprague-Dawley Crl:CD^{R}BR Rat Carcinogenicity Study.

Reference: J.A. Trutter: "Combined Chronic Toxicity and Oncogenicity Study in rats with Omite technical". Hazleton Laboratories #798-220, January 11, 1991. MRID # 417509-01. Classification: Guidelines.

a. Experimental Design

The basic experimental design for this study consisted of dosing five groups of 50 rats per sex with either 0, 50, 80, 400 or 800 ppm (corresponding to 2.38, 3.83, 19.24 and 38.87 mg/kg/day, respectively, for males and 2.95, 4.68, 23.58 and 49.36 mg/kg/day, respectively, for females) of propargite for a scheduled 2 years. Additional groups of 10 rats/sex/dose were included but sacrificed at week 53 of dosing. In the later weeks of the study (after week 96), there was an apparent compound related increase in deaths among the male

mid and high dose groups and the study for males was terminated one week ahead of schedule.

b. Discussion of Tumor Data

Tables 1 and 2 show that the mid and high dose males and high dose females had statistically significant increased incidences of undifferentiated sarcomas in the jejunum.

There were no specific organ tumors in the stomach or duodenum, cecum, ileum, colon or rectum. There were 2 incidents of undifferentiated sarcoma in the ileum in the male high dose group, but these animals (#555 and 534) also had the tumor in the jejunum.

Undifferentiated sarcoma (a tumor of mesodermal origin) of the gastrointestinal tract is a rare tumor in rats. In the historical control data only one male rat out of 472 (in 9 studies) had this condition in the duodenum and none in the jejunum out of 455 animals. No females had this type of tumor out of 479 (duodenum) and 465 (jejunum) animals. Because of the rarity of this tumor, the females in the 50, 80 and 400 ppm dose groups which had a single incident each may be also affected by the test material.

Propylene oxide, a known mutagen and carcinogen, was used as a stabilizer in early batches of propargite. The registrant, through its consultant (Dr. Robert Squires), has suggested that the combination of ulcerative effects of propargite and the presence of the known mutagen propylene oxide in the test material may have resulted in the tumors. However, the PRC concluded that the tumors were unlikely to be due to the combination of ulcerative effects of propargite and propylene oxide since there was no clear compound-related increase in duodenal or jejunal ulcers or other signs of irritation seen in this study. Also, the effect of propylene oxide would be expected to be on the epithelial lining of the intestine; the tumors were mesodermal in origin. Further, it was considered equally possible that the ulcers seen with some of the tumors were a result of the tumor, not a cause of it.

The registrant has initiated a second study in rats which tests propargite with [redacted] as the stabilizer rather than the propylene oxide. This study is not expected to arrive at the Agency for an estimated 2 more years.

Table 1. Propargite - Sprague-Dawley Male Rats, Jejunum Tumor Rates+ and Peto's Prevalence Test Results (p values)

	Dose (ppm)				
	0	50	80	400	800
Tumor undiffer-entiated sarcomas	0/42	0/46	0/44	11/44	24[a]/45
(%)	(0)	(0)	(0)	(25)	(53)
p=	0.000**	1.000	1.000	0.003*	0.000**

+ Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[a] First sarcoma observed at week 65, dose 800 ppm.
Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If * then $p<0.05$ and if ** then $p<0.01$.

Table 2. Propargite - Sprague-Dawley Female Rats, Jejunum Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	0 ppm	50 ppm	80 ppm	400 ppm	800 ppm
Tumor undiffer-entiated sarcomas	0/45	1/48	1/49	1/48	12[a]/44
(%)	(0)	(2)	(2)	(2)	(27)
p=	0.000**	0.516	0.521	0.516	0.000**

+ Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.
[a] First sarcoma observed at week 67, dose 800 ppm.
Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level.
If * then $p<0.05$ and if ** then $p<0.01$.

c. Non-neoplastic Lesions and Other Observations

There was a positive statistical trend ($p < 0.01$) for increased mortality in the males. This decrease in survival, although not statistically significant by pairwise comparison, was apparent among the males in the 400 (19.24 mg/kg/day) and 800 ppm (38.87 mg/kg/day) groups after week 96.

Non-neoplastic findings in the stomach, duodenum and ileum were occasional and not compound-related in a dose-dependent manner. For example, the incidence of "ulcer" in the glandular stomach was 4, 4, 5, 7, 11 for the males and 7,6,3,3,4 for the females for the control to high dose groups respectively (out of 60 animals per group). Mucosal gland dilation of the glandular stomach was present in many rats. In the males, 60, 43, 45, 65, and 69% were affected in the controls to high dose groups, respectively, and in the females, 68, 61, 75, 71 and 77% were affected. Mucosal gland dilation in the duodenum was noted in 1 high dose male and not in other male groups and in 3 high dose females but only one in the other female groups. There were 2 incidents of chronic inflammation in the high dose female group but none in any other group. Nonneoplastic lesions in the cecum, colon and rectum were few in number (2 or less except for parasitism). There were no lesions of any kind reported in the esophagus. No information on the mouth was presented.

Body weight gain decreases in males (to -9% at 400 ppm and to -30% at 800 ppm between weeks 0-6) and females (800 ppm to -26.3% between weeks 0 to 6) were the most obvious non-neoplastic effects noted. The maximum decrement in female weight gain (-41.1%) was during the interval between weeks 13 to 28. Absolute body weight was about 6% or less than the control for the mid dose and about 12.5 - 17.5% less for the high dose males. Female body weights for the mid dose group were 4% less than the controls while for the high dose group they were 10 - 19% less than the controls. The body weight and body weight gain data support a NOEL/LEL of 80/400 ppm in males and 400/800 ppm in females.

There were also slight decreases in serum total protein and Ca++ for males at 400 ppm and above. At 800 ppm there was noted an apparent transient decrease in globulin and increase in albumin/globulin ratio.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Based on decreases in weight gain in the mid and/or high dose groups for both males and females, the dose levels are considered adequate for assessing the carcinogenic potential. The PRC notes that some may consider the high dose level excessive based on the 30% or greater decrease in body weight gain in the high dose males. However, since tumors were noted at lower dose levels, the weight gain effects are not considered by the PRC to compromise the significance of the carcinogenicity assessment.

2. FDRL Strain Carcinogenicity Study

Propargite was evaluated for potential carcinogenicity in an earlier rat study (FDRL # 86000 and 86014, December 26, 1966). No HED DER was prepared for this study. The basic design of this study consisted of dosing 25 rats/sex (FDRL strain) with 0, 5, 15, or 45 mg/kg/day for 2 years and an additional 25/sex at 100 mg/kg/day for 18 months. The study report author and the EPA reviewer concurred that the NOEL was > 45 mg/kg/day and there were no compound-related increases in neoplasms reported. Certain deficiencies in the pathology report were noted and there were an insufficient number of animals per dose group. Thus, the data are considered Supplementary.

3. CD-1 Mouse Carcinogenicity Study

Reference: G.E. Cox and T.A. Re "Chronic oncogenic evaluation of Omite in CD-1 mice following 78 weeks of dietary treatment" Food and Drug Research Laboratories, Inc (FDRL) Feb 8, 1979 Study No. 5036. MRID No. 00130942. Classification: Supplementary.

a. Experimental Design

The basic study design consisted of dosing 5 groups of 60 CD-1 mice per sex with either 0, 50, 160, 500 or 1000 ppm (estimated to be 0, 7, 23, 71 and 143 mg/kg/day) of propargite for 18 months. Additional groups of 15 mice per sex per dose group were dosed with 0, 500 or 1000 ppm for one year. Propylene oxide was used as a stabilizer.

b. Discussion of Tumor Data

There were no apparent increases in tumors associated with increases in the dose level of propargite, even though propylene oxide was included.

c. Non-neoplastic Lesions

There were no effects on growth (body weight) or hematology. Possible effects on the weights of the kidney, adrenals, thyroid and uterine weights were mentioned but these were not supported by histopathological changes.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dose levels were selected on the basis of a range finding study in which 10 mice/sex were dosed with either 0, 600, 900, 1350, 2000 or 3000 ppm for 30 days. The authors of this study believed that this study showed that the mice dosed with 1350 ppm and above had decreased food consumption and body weight loss and decreased ovary weight. Kidney weights were decreased in the 2000 and 3000 ppm dose groups and 5 mice in the 3000 ppm dose group died. The authors determined that a dose of 1000 ppm should be appropriate for the definitive study.

However, the PRC determined that the mice could have tolerated higher doses than 1000 ppm because the apparent weight effects were barely evident at 1350

ppm and occurred only in the first few days of the range finding study. Since there were no definite effects noted in the carcinogenicity study, the dose levels were considered by the PRC to be too low to adequately assess for carcinogenicity. The range-finding study indicated that the MTD was 2000 ppm or 3000 ppm. Thus, the tested dose was only 1/2 to 1/3 of the adequate dose for carcinogenicity testing.

Also the mice in the 18 month study were initiated on their test diets containing propargite when they were 12 weeks of age. The Guidelines stipulate that in no case rodents should not be greater than 8 weeks of age at the start of dosing.

E. Additional Toxicology Data on Propargite:

1. Metabolism

The absorption, elimination and tissue distribution of propargite have been studied in a series of experiments using rats and to a limited extent with mice. An overview of the metabolism of propargite has been prepared by TB-I and can be found in Document No.: 008969.

In summary, the urinary route is the predominant route of elimination in the males (61.1%); females eliminate less by this route (49.7%) following a low dose (25 mg/kg). Following a high dose (200 mg/kg), the fecal route is the major route of elimination (69.9% for females and 74.5% for males). Peak excretion was noted in 6-24 hours when 75-80% of the low dose was eliminated. The respiratory route is not considered important (0.04% excreted in 24 hours). The biliary route is also of minor importance since only 6.1% of the dose was excreted in the rat and 0.02% and 0.7% were excreted in the rabbit and monkey respectively.

Tissue retention data indicated the liver, kidney and gastrointestinal tract retained the highest levels of radioactivity following a dose of 25 mg/kg. Only 1.6% of this dose was retained in the tissues after 96 hours in rats.

Six metabolites were identified. The metabolism of propargite has been demonstrated to proceed by hydrolysis to remove the sulfite moiety. The remaining phenoxy cyclohexyl moiety is further hydroxylated on the cyclohexyl ring, and/or oxidized at the methyl ring to an alcohol and/or carboxylic acid subsequently conjugated and excreted.

2. Mutagenicity

Summary of Mutagenicity/Genetic Toxicity Studies with Propargite.

Study	Results
Microbial assays (Salmonella and Saccharomyces indicator organisms). Litton Bionetics #2683, May, 1977. MRID No.: 00066497. Classification. Not classified according to current criteria.	Not demonstrated to be positive in presence or absence of metabolic activation (rat liver microsomes).
Gene Mutation in Mammalian Cell Cultures (CHO/HGPRT) Pharmakon International, Study No.: PH 314-UN-001-87, October 13, 1987. MRID No.: 403846-01 Classification: Pending.	Positive for inducing forward mutation at the HGPRT locus in non-activated (but not in activated) cultures of Chinese hamster ovary cells up to 1.0 ug/ml without activations and 15.0 ug/ml with activation by S9.
in vivo Mouse micronucleus test. Pharmakon International, Study No.: PH 309-UN-001-87, Sept. 29, 1987. MRID No.: 403846-03 Classification: pending	Negative for inducing micronuclei in bone marrow polychromatic erythrocytes of mice treated with single i.p. doses at levels up to 150 mg/kg.
Other Genotoxicity (DNA Damage/Repair in vitro (HPC/UDS). Pharmakon International Study No.: PH 311-UN-001-87 July 9, 1987. MRID 403846-02. Classification: Pending	Negative for induced unscheduled DNA "repair" synthesis (UDS) in rat hepatocyte cultures (HPC) exposed just below cytotoxic doses 1.67 ug/ml.

One study, gene mutation in mammalian cell culture with Chinese hamster ovary cells, is considered positive in the absence but not in the presence of the S-9 metabolic activation system. The non-activation was reproducible over several replicate experiments. This indicates that the substance is a direct-acting mutagen. This CHO test would fulfill the need for the gene mutation study for the purpose of mutagenicity testing.

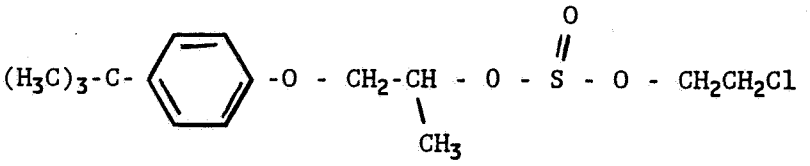
The PRC recommends a new micronucleus study using a multi-dosing regime over several days. This is necessary to clarify conflicting results from the submitted mouse micronucleus study since there was a clear, positive response in the first experiment which was not replicated in the second experiment. Also, in order to illuminate possible mechanisms of action, another Salmonella test is also recommended with alternative activation systems (e.g. include alcohol dehydrogenase).

3. Developmental Toxicity

Propargite was reviewed twice by the Developmental and Reproductive Toxicity Peer Review Group. Developmental toxicity, in the form of sternebral defects, was found in the rabbit. The NOEL for this effect is 8 mg/kg/day, a level which also induces maternal toxicity. Propargite induces only equivocal developmental toxicity in the rat at dose levels which also induce maternal toxicity (105 mg/kg/day).

4. Structure-Activity Correlations

Propargite is a sulfite which can be considered to be structurally related to aramite (2-chloroethyl 1-methyl-2-(p-tert-butylphenoxy)ethyl sulfite).



Structure of Aramite

Aramite has been demonstrated to be associated with gallbladder and bile duct adenocarcinomas in dogs, nodular liver lesions and hepatocellular carcinomas in rats and "hepatomas" in mice.[2] No information on a relationship between aramite and increased incidence of undifferentiated sarcoma in the jejunum was indicated in the study report summaries.

A computer survey of two data bases (CIS and TOXNET) of the literature using the structure of propargite did not indicate additional toxicity information.

5. Acute, Subchronic, and Chronic Toxicity Studies

Propargite has a low order of acute toxicity by the oral route (estimated 1.89 gm/kg and higher in rats and > 5 gm/kg in monkeys) and dermal (> 2 gm/kg to rabbits) routes. Inhalation LC_{50}s of > 2 mg/l have been reported. Several studies indicate that propargite results in corneal opacity that persists through 7 or 14 days. Other studies indicate that propargite is a dermal

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[2]Innes JRM, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorgenicity in mice: a preliminary note. Nat. Cancer Inst. 42:1101-1114.

Popper H, et al. 1960. The carcinogenic effects of aramite in rats. Cancer 13:1035-1046

Steinberg S, et al. 1960. Gallbladder and bile duct adenocarcinomas in dogs after long term feeding of aramite. Cancer 13:780-789.

irritant (PIS = 7.1/8.0). Two studies (one with a formulation) did not indicate that propargite was a dermal sensitizer in guinea pigs.

Oral subchronic studies with rats indicate a NOEL/LEL of 40/100 mg/kg following 3 months of dosing and a dog study demonstrated a NOEL < 2000 ppm (estimated 50 mg/kg/day, only dose tested). The chronic feeding studies are considered to better evaluate the oral toxicity in these species. A three week dermal toxicity study in rabbits indicated a NOEL/LEL of 10/100 mg/kg/day based on increased segmented neutrophils. This reaction is considered a possible response to the local irritation and scarring caused by propargite which was noted at all doses (0.1 mg/kg, lowest dose tested).

The signs of toxicity noted in the more recent (1991) chronic feeding rat study were indicated above. An older study FDRL, #86000 and 86014, December 29, 1966, MRID No.: 90718, Document Nos. 1890, 3484, 1410, 4488 and 4489) was concluded to have a NOEL > 900 ppm the highest dose tested (estimated 45 mg/kg/day.

The NOEL/LEL for the dog chronic feeding study (Bio/Dynamics, Inc. #88-3377, January 10, 1991, MRID # 417514-01, Document No.: 8715) were determined to be 5/38 mg/kg/day based on decreased weight gain and blood counts, increased stomach parietal cell vacuolization and gland dilation. An older dog study (FDRL #86000 and 86014, December 29, 1966, MRID No.: 0990718, Document Nos.: 3483, 1410 and 4219) has also been reviewed and demonstrated to have a NOEL of 900 ppm (HDT estimated 22.5 mg/kg/day).

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on propargite in a weight-of-the-evidence determination of carcinogenic potential.

1) In male Sprague-Dawley rats, propargite was associated with statistically significant increases in undifferentiated sarcomas in the jejunum (and ileum) at dose levels of 400 (25% affected) and 800 (53%) ppm. There was also a statistically significant increase in trend.

2) Female rats had sarcomas in the jejunum at doses of 50 (2%), 80 (2%), 400 (2%) and 800 (27%) ppm. Although the females had only 1 tumor/per group at the three lower doses, the PRC considered these tumors to be biologically significant. There was a statistically significant increase in trend, and an increase in the pair-wise comparison at the HDT (800 ppm).

3) The historical control data revealed 0 incidence of undifferentiated sarcomas in the jejunum in about 500 rats of each sex from 9 separate studies.

4) The dosage levels for the rat study were considered appropriate. Larger decreases in weight gain in the high dose groups were not considered to be sufficiently severe to compromise the interpretation of the study data.

5) There were no compound-related neoplasms in a 18 month rat study by FDRL, performed in 1966. However, this study was inadequate due to insufficient numbers of animals and deficiencies in the pathology report.

6) Propargite was not associated with increases in tumors or systemic effects in a carcinogenicity study with CD-1 mice. However, this study was limited due to the lack of systemic effects indicating a lack of adequate dosing and due to the older age of the mice at the time of the start of dosing (12 weeks rather than the recommended 8 weeks).

7) Propargite was demonstrated to be mutagenic in a Chinese hamster ovary cell gene mutation study in the absence but not presence of metabolic activation. No consistent evidence that propargite was mutagenic or genotoxic was derived for bacterial mutagenicity studies (older study), or an unscheduled DNA repair study. Propargite produced positive and negative results in two replicate experiments, respectively, for micronuclei in mouse bone marrow. These data provide evidence for a mutagenicity concern. This would support a carcinogenicity concern.

8) Propargite is structurally related to aramite which has been demonstrated to cause tumors in rats, mice, and dogs in the liver, gall bladder and/or bile duct. The target sites for tumors associated with aramite are not similar to that for propargite.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The Peer Review Committee agreed that the classification for propargite should be Group B2- possible human carcinogen.

This decision was based on the fact that the rat study alone provided sufficient evidence of carcinogenicity since a rare (unusual site) and malignant tumor was produced with a high incidence. Statistically significant increases in undifferentiated sarcomas in the jejunum of male and female rats were observed at several dose levels. Although the females had only one tumor in each of the 3 lower dose groups, the PRC concluded that these incidences were biologically significant. Both male and female rats showed a dose-response and increased trend for increased tumors. This type of tumor is malignant, rare, and fatal. This study was conducted using adequate doses for the determination of carcinogenic activity. The highest dose tested caused excessive decreases in body weight gain. In males, though, there was a statistically significant increase in tumors at the next highest dose level, which was not an excessive dose.

Propargite was not associated with increases in tumors or systemic effects in a carcinogenicity study with CD-1 mice. However, this study was determined to be inadequate.

Since propargite is now classified as Group B2, the PRC does not see the need to recommend a new mouse study at this time. If for any reason, the classification is reevaluated, the need for another mouse study will also be reevaluated. No reevaluation is being considered at this time.

Propargite was determined to have mutagenic activity, although the database is incomplete. A structurally related compound, aramite, has been shown to be carcinogenic in three species.

The PRC understands that the registrant may be performing another rat study which does not use propylene oxide. The registrant claims that commercial technical propargite no longer uses propylene oxide as a stabilizer. If a new rat study has negative results, this study alone will not be sufficient to overturn the Group B2 classification.

For determination of the Q_1*, the PRC recommends use of a low-dose extrapolation model using data from both male and female rats. A geometric mean should be taken from these two analyses to determine the Q_1*. The fatal tumor analysis should also be reviewed.