

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

**BENTAZON/BENTAZON SODIUM**

Chemical Code # 2999/1944, Tolerance # 355  
SB 950 # 220

Original date: July 21, 1986  
Revised: Mar. 26, 1987; March 28, 1996; and September 30, 1999

I. DATA GAP STATUS

Combined (chronic + onco) rat:	No data gap, possible adverse effects <sup>1</sup> (not onco)
Chronic dog:	No data gap, possible adverse effects
Onco rat:	(see Combined rat)
Onco mouse:	No data gap, possible adverse effects
Repro rat:	No data gap, possible adverse effects
Terato rat:	No data gap, possible adverse effects
Terato rabbit:	No data gap, possible adverse effects
Gene mutation:	No data gap, no adverse effects
Chromosome:	No data gap, no adverse effects
DNA damage:	No data gap, no adverse effects
Neurotox:	Not required at this time

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<sup>1</sup> Rereview identified the eyes and optic nerves as target organs in record 042993 (discussed in worksheet W042993.S01)

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**Note: Toxicology one-liners are attached**

\*\* indicates acceptable study

**Bold face** indicates possible adverse effect

Revised file name: t990930  
Revised by: Stephen J. Rinkus, 9/30/99

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects. When the Summary of Toxicology Data was revised in 1987, that revision was produced using the CompuPro system. However, the 1987 revision was not transferred to the subsequent system (Prime). As a result, in order to revise the Summary of Toxicology in 1996, it was first necessary to reenter the last version, which was one dated March 26, 1987. The decision was made in 1996 to reenter that Summary of Toxicology essentially word for word, without excluding references to obsolete filenames and correcting typographical errors. In the case of the two rodent chronic exposure studies (record 042993 & associated records; record 043271 and associated records), their one-liners were revised after rereviews were completed. This was done in order to bring the completeness of the one-liners up to the level found in the USEPA Reregistration Eligibility Decision document (EPA 738-R-94-029) for Bentazon, which had been issued in 1994. (Rinkus, 9/30/99).

### SUBCHRONIC TOXICITY, RAT

**Note:** Three rat studies of one-to-three month durations apparently are not on file with DPR. 1) The dose levels used in the 2-year chronic toxicity/oncogenicity rat study (record 042993) were selected based on the results of a one-month pilot feeding study. Dose levels in that pilot study were: 0 ppm, 600 ppm, 1800 ppm, 5000 ppm and 10,000 ppm. Hemorrhagic lesions, apparently involving the urogenital organs, were seen in rats exposed to  $\geq 5000$  ppm. It has been requested that this study be submitted if the Registrant chooses to revisit the identification of the eyes and optic nerves as target organs in record 042993. 2) A 13-week feeding study using Wistar rats is mentioned in the USEPA's Reregistration Eligibility Decision document (EPA 738-R-94-029) for Bentazon. Dose levels were: 0 ppm, 400 ppm, 1200 ppm and 3600 ppm. Effects were said to include: reductions in bodyweight gain; increased thromboplastin times and prothrombin times; diuresis; increases in albumin, A/G ratios, and sodium; increased kidney and liver weights; and suggestive evidence in the females of lung thrombi and dilated uterine horns. 3) In the 13-week feeding study summarized below (record 970019), mention was made of a 28-day feeding study, wherein changes in the testes possibly were seen. (Rinkus, 3/28/96).

**355-028 970019**"90-Day feeding trial on rats with 3-isopropyl-2,1,3-benzothiadiazinone-(4)-2,2-dioxide." (H. Zeller & P. Kirsch; Medicinal-Biological Research Lab., BASF AG; no report identification number; July 22, 1970). Bentazon (Reg. No. 51 929; technical grade, otherwise purity not defined) was administered in the diet to 20-30 Sprague-Dawley rats/sex/dose level for 90 days at 0 ppm, 70 ppm, 200 ppm, 800 ppm and 1600 ppm. In the "postexposure" part of the study, 9-10 rats/sex/dose for the dose levels of 0 ppm, 70 ppm and 1600 ppm were taken off their Bentazon diets after 90 days and given Bentazon-free feed for the next 6 weeks. No effects in either sex were noted on survival, food consumption (note: no water intake determinations), bodyweight, the absolute weights and organ weight-to-bodyweight ratios for the liver, kidney and heart; urinalysis (note: no volume or specific gravity determinations); platelet counts; prothrombin times (note: no APTT determinations); or the incidences of neoplastic and nonneoplastic lesions. The only suggested treatment-related effects were the following: increased hematocrit in testing done at day ~30 (1600 ppm males and females) and at day ~70 (800 ppm and 1600 ppm males; 1600 ppm females); and increased blood urea in testing done at day ~30 (800 ppm and 1600 ppm males; 1600 ppm females) and at day ~70 (800 ppm and 1600 ppm males). **Supplemental information. No worksheet.** (Rinkus, 3/28/96).

### COMBINED CHRONIC TOXICITY/ONCOGENICITY, RAT

**\*\*043-046 43273-43275, 42993, 42995, and 43259.** "Studies on the 24-month oral chronic toxicity and potential carcinogenicity of Bentazon in rats". (Takehara *et al.*; Nippon Institute for Biological Science, Tokyo, Japan; no report identifier on record 042993; date of signatures = Nov., 1984). (The original one-liner was revised to the following based on a rereview). Bentazon (the free acid), 93.3% purity, was administered in the diet at 0 ppm, 200 ppm, 800 ppm and 4000 ppm to 70 Fischer 344/Du Crj rats/sex/treatment level for up to 2 years. Dose levels were selected based on the results of a one-month pilot study that was not included in this report. Interim sacrifices were performed at 27 weeks and 53 weeks, using ~10 rats/sex/treatment level. These same groups were used to generate the 6-month and 12-month data in the areas of hematology, serum chemistry, urinalysis, ophthalmology, etc. No effect on survival was noted. Bodyweight reduction to ~92% and ~87% of the control values was seen in the male and female 4000 ppm groups, respectively, between test weeks 53-78; no bodyweight effect was seen in the lower dose groups (both sexes). Water intake was increased in a dose-and-time-dependent fashion in the 800 ppm and 4000 ppm groups (both sexes). Frank polyuria was seen at 6 months and 12 months in the 4000 ppm groups (both sexes) and a lesser effect was seen at 6 months in the 800 ppm groups (both sexes). The specific gravity of the urine was decreased in a dose-dependent fashion in the 800 ppm and 4000 ppm groups at 6 months (both sexes) and 12 months (males). Blood urea nitrogen was increased in a dose-dependent fashion in the males at 6 months and was increased in the 4000 ppm female group at 6 months and in the 800 ppm and 4000 ppm female groups at 12 months. Serum glucose was decreased in the males at 6 months (200 ppm and 800 ppm), 12 months (4000 ppm) and 24 months (200 ppm and 4000 ppm) and in the females at 24 months (200 ppm and 4000 ppm). Absolute and relative kidney weights were increased at 6 months and 12 months in the 4000 ppm groups (both sexes). Absolute and relative thyroid weights were decreased at 6 months and 12 months in the 800 ppm and 4000 ppm male groups. Activated partial thromboplastin times were increased in the males at 6 months (4000 ppm), 12 months (800 ppm and 4000 ppm) and 24 months (4000 ppm) and in the females at 12 months (800 ppm and 4000 ppm). Prothrombin times were increased in the 4000 ppm males at 6 months and 12 months. Platelet counts were decreased at 6 months in the 800 ppm and 4000 ppm male groups and in the 4000 ppm female group. Hemoglobin concentration was increased in the males at 6 months (800 ppm and 4000 ppm) and 12 months (4000 ppm) and in the females at 12 months (4000 ppm). The incidence of pituitary cysts was increased in the 4000 ppm female group. Rereview of the data related to the eyes and optic nerves indicates that these organs were affected in the 4000 ppm male group, with an incipient effect also occurring in the 4000 ppm female group. The clinical observation data indicate that 32% (16/50) and 26% (13/50) of the males in the 4000 ppm main group exhibited enlargement of the anterior chamber of the eye and opacity of the eye, respectively; the corresponding incidences in the female 4000 ppm main group were 6% (3/50) and 2% (1/50). No other male or female in the 0 ppm, 200 ppm or 800 ppm groups exhibited enlargement of the anterior chamber of the eye; and only one rat from these groups (a 200 ppm male) had opacity of the eye as a clinical observation finding. Clinically affected rats often exhibited other major effects: cataracts, keratitis/corneitis; cloudy eyeball; optic nerve atrophy; optic nerve degeneration (based on histological examinations of only ten 4000 ppm males); and the severe grade of retinal lesions. In many respects, the pathogenic process suggested by these findings is glaucoma. No evidence of carcinogenicity was seen in either sex. **NOAEL = 200 ppm (increased water intake, polyuria, decreased specific gravity of the urine, increased BUN, thyroid weight decrease, increased APTT, platelet decrease, increased hemoglobin).** This study is **ACCEPTABLE**. Supplemental information (described in worksheet W042993.S01) will need to be submitted in order to revisit the new adverse effect identifications regarding the eyes and optic nerves. (Rinkus, 3/7/96).

029 970023 Invalid Cannon Labs study. No useful data.

053 55186 (Review of N.I.B.S. eye and brain histology data by W.H. Butler. This record is identical

to 043:042995, except that the present record includes a title page to orient the reader).

### SUBCHRONIC TOXICITY, DOG

**Note:** Mention is made in record 970008 (volume 355-002) of a 28-day dog dietary study that tested dose levels of 0 ppm, 3000 ppm and 6000 ppm, apparently using 2 dogs/sex/dose. Effects were said to include: weight loss in the 6000 ppm females and testicular degeneration in the 6000 ppm males. This study presently is not on file at DPR. (Rinkus, 3/28/96).

**355-028 970020**"13-Week toxicity of 3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide to beagles when administered with the food" (Leuschner *et al.*; Laboratory of Pharmacology and Toxicology, Hamburg, Hausbruch; no report identification number; 9/28/70). Bentazon (referred to as XIX/410; purity not stated) was homogenized into dog feed on a daily basis at concentrations of 0 ppm, 100 ppm, 300 ppm, 1000 ppm and 3000 ppm (note: no analytical testing). Each dog (3 beagles/sex/dose) received a daily ration of 40 g feed/kg bodyweight for 13 weeks. The respective doses on a mg/kg-d basis (both sexes) were: 0, 4, 12, 40 and 120 (until feed consumption decreased, starting about test week 6). Deaths occurred only in the 3000 ppm groups: one male died in test week 11; and two females died in test weeks 12 and 13. Bodyweight was affected only in the 3000 ppm groups: two males and the three females each lost about 1 kg in bodyweight over the 13-week exposure period. Clinical findings in the 3000 ppm groups included: sedation, starting within 1 h after feeding and lasting from two to 24 hours (onset in weeks 2 and 3 in the males vs. in week 5 in the females; the time asleep increased as the study progressed); vomiting (males only; onset in week 3); bilateral hemorrhagic conjunctivitis (onset in week 4 in the males vs. in week 8 in the females); diarrhea (onset in week 5 in the males vs. in week 8 in the females); decreased feed consumption (onset in week 6 for both sexes); stomatitis (males only; onset in week 6); and episodes of tremors and (or) ataxia (onset in the second half of the study for both sexes). In the case of two 3000 ppm males, blood was seen in the diarrhea towards the end of the study. Water intake was said to have been normal although no data were provided. Ophthalmological examinations using a Gullstrand's slit lamp only identified the conjunctivitis in the 3000 ppm dogs as a finding. Hematological effects were seen only in the 3000 ppm groups. These included: reductions in hemoglobin concentration, red blood cell count, and packed cell volume (both sexes at weeks 6 and 13); increased prothrombin time (both sexes at weeks 6 and 13); and decreased platelet count (females at week 6; one of two males at week 13)(note: activated partial thromboplastin times were not studied). Serum chemistry effects were seen only in the 3000 ppm groups. These included: increased SGPT and SGOT (same female at week 6; one of two males and the lone female at week 13); increased alkaline phosphatase (one female at week 6; both males and the lone female at week 13); increased blood urea nitrogen (equivocal effect in females at week 6; equivocal effect in the males and the lone female at week 13); increased total bilirubin (one female at week 6; both males and the lone female at week 13); and decreased total protein (both sexes at weeks 6 and 13). Serum electrolyte effects possibly present at week 13 included: increased chloride in the lone 3000 ppm female; and decreased potassium in both 3000 ppm males. Urinary effects included: traces of ketones (3000 ppm groups [both sexes] at weeks 6 and 13); proteinuria (one 3000 ppm female at week 6; both sexes at week 13); increased potassium (one 3000 ppm male at week 13); increased sodium (equivocal effects in the 300 ppm and 1000 ppm female groups at week 6; single males affected in the 300 ppm, 1000 ppm and 3000 ppm groups at week 13); and increased specific gravity of urine (two 3000 ppm males). Gross pathology effects only were seen in the 3000 ppm groups. These included: pale liver (both sexes); liver with marked or maculate lobes (males); and pale kidneys (the three females, two of the males). Whether organ weights were affected could not be discerned from the report since no absolute organ weight data were provided and organ-to-bodyweight ratio data were not interpretable in the 3000 ppm dogs due to their reduced bodyweights. Possible histological effects included: slight fatty degeneration in the myocardium (one 3000 ppm male, two 3000 ppm females); slight to marked fatty degeneration in the liver (two 3000 ppm males, three 3000 ppm females); and prostatitis, sometimes involving pus formation (one 100 ppm male, one 300 ppm male, three 3000 ppm males). **Supplemental information. No worksheet.** (Rinkus, 3/28/96).

## CHRONIC TOXICITY, DOG

**\*\*355-067 073506** "52-Week Oral Toxicity (Feeding) Study with Bentazon Technical (ZST No. 86/48) in the Dog" (Allen *et al.*; RCC Research & Consulting Co. AG; RCC project no. 067746; Feb. 24, 1989 [April, 1989 for amendment 1 [record 074558]). Bentazon (not the sodium salt), 98% purity, was administered in the diet at 0 ppm, 100 ppm, 400 ppm and 1600 ppm to six beagle dogs/sex/dose for 52 weeks, resulting in Bentazon intakes at the end of the study of 0, 3, 13 and 47 mg/kg-d for the males and 0, 3, 12 and 53 mg/kg-d for the females, respectively. All dogs on test survived until the end of the study although one 1600 ppm male had its exposure to Bentazon stopped during test week 7 for six days when bloody diarrhea and hematology changes were observed. Possible treatment-related effects were seen with the 1600 ppm groups and included the following: intermittent hematology effects involving 3-4 dogs/sex (decreases in red blood cell counts, hemoglobin concentration and/or hematocrit; increases in thromboplastin and/or partial thromboplastin times; abnormal red blood cell morphology); testicular effects (decreased spermiogenesis and tubular degeneration); decreased total bilirubin in males (test weeks 26 & 52); decreased alkaline phosphatase in females (test weeks 13, 26 & 52); and decreased specific gravity of the urine from the females (test week 52). In the four females from the 1600 ppm group that were examined, each exhibited glandular proliferation of the mammary gland and one was actively secreting. By contrast, only one of the six control females exhibited the former. The 100% (4/4) incidence of glandular proliferation raises the possibility of a hormonal imbalance in the 1600 ppm females. **NOEL = 400 ppm (intermittent hematology changes; decreased spermiogenesis or tubular degeneration in the testes; possible hormonal imbalance; decreased total bilirubin, decreased alkaline phosphatase, decreased specific gravity of urine)**. When first reviewed (Rinkus, 11/1/95), this study was considered unacceptable and the histological examination of the ovaries was requested (discussed in worksheet W073506.831). Subsequently, the Registrant submitted record 150398, which contained historical negative-control data for ovary weights and lesions in the mammary gland and testes. This study is now considered marginally **ACCEPTABLE**, with the following "conservative call." A possible hormonal imbalance in the 1600 ppm female group is assumed, based on a 100% incidence of glandular proliferation in the mammary gland. Reconsideration of this "conservative call" will require the histological examination of the ovaries and submission of the supplemental information described in worksheet W073506.S01. (Rinkus, 9/16/99).

355-079 150398 This record was submitted in response to worksheet W073506.831. It consists of the following: 1) three pages of narrative discussing ovary-weight data and historical negative-control data from the conducting laboratory regarding ovary weights, glandular hyperplasia in the female mammary gland and tubular degeneration in the testes; 2) individual ovary data from record 073506 (absolute and relative to necropsy bodyweight); 3) three tables summarizing negative-control data from 22 studies conducted between 1983 and 1992; 4) a summary table of ovarian-weight data for 54 untreated dogs; and 5) individual ovarian weights for 54 untreated dogs, representing 11 studies. These data are discussed in worksheet W073506.S01. **Supplemental information.** (Rinkus, 9/30/99).

## SUBCHRONIC TOXICITY, MOUSE

**Note:** Mention is made in record 043271 (volume 355-041) of an one-month mouse dietary study that tested dose levels of 0 ppm, 400 ppm, 2000 ppm, 5000 ppm and 10,000 ppm. It was stated that some mice in the 5000 ppm group died and had hemorrhagic lesions (site not stated). This study presently is not on file at DPR. (Rinkus, 3/28/96).



## ONCOGENICITY, MOUSE

**Note:** 1) A memorandum from Jim Carlisle (Risk Assessment Group) to Larry Nelson (former Branch Chief), dated March 17, 1987, indicates that based on the liver histology data of Dr. Carlton in record 055398, there is a statistically significant dose response in the male mice in record 043271 for adenomas and for adenomas plus carcinomas. 2) Mention is made in record 068221 (volume 355-039) of an oncogenicity study, that apparently was done at Huntingdon Research Centre, England, in the 1970's, using CFLP mice. This study presently is not on file at DPR. 3) A metabolism study in mice (record 970038, volume 355-025) suggests that mice metabolize Bentazon to a greater degree than rats. (Rinkus, 3/28/96).

**\*\*041-042 043271, 043272, 042992, 042994 and 043260 [355-059 055398 contains data from blind rereading of liver and lung slides].** "Studies on the 24-month chronic toxicity of Bentazon Reg. No. 51 929 (ZNT No. 81/273) in mice." (K. Takehara [study director & translator of report from Japanese into English]; Nippon Institute for Biological Science, Tokyo, Japan; no report identifier on record 043271; date of the original Japanese report = 3/21/84). (The original one-liner was revised to the following based on a rereview). Bentazon (the free acid), 93.9% purity, was administered in the diet at 0 ppm, 100 ppm, 400 ppm and 2000 ppm to 70 B6C3F1 mice/sex/treatment level for up to 2 years. Dose levels were selected based on the results of a one-month pilot study that was not included in this report. Interim sacrifices were performed at 27 weeks and 53 weeks, using ~10 mice/sex/treatment level. These same groups were used to generate the 6-month and 12-month data in the areas of hematology, serum chemistry, urinalysis, ophthalmology, etc. Survival at the end of the study for the male and female groups ranged from 60-72% and 70-82%, respectively. The 2000 ppm groups (both sexes) exhibited the lowest survival, but neither reduction was statistically significant. No effect on the bodyweights of the female groups was seen and although the bodyweight of the 2000 ppm male group in the first quarter of the study was reduced in some weeks to 96% of the corresponding control value, this was of doubtful toxicological importance. Summary tables indicated that there was no significant effect on the incidence of clinical signs, but individual clinical data were not provided in the report. No significant effects on food consumption, water intake or ophthalmology findings were noted in either sex. Effects in urinalysis testing were limited to the following: a statistically significant increase in the specific gravity of the urine for the 400 ppm and 2000 ppm male groups tested at 12 months; and the finding of occult blood in the urine of three of the ten 2000 ppm males tested at 24 months (versus no occult-blood cases among the 30 males that made up the other groups). Slight reductions in the red blood cell count seen at 6 months in the 400 ppm male group and in the three Bentazon-exposed female groups were not present in the testing done at 12 months and 24 months. Prothrombin time, which was assayed only at 24 months using ~7 mice/sex/group, was statistically increased in the 400 ppm and 2000 ppm male groups; increases in the activated partial thromboplastin time paralleled the changes in prothrombin time but did not achieve statistical significance. Statistically significant effects in the limited blood chemistry testing done at 24 months included: an increase in the albumin/globulin ratio in the 2000 ppm male group (accompanied by a reduction in total protein that did not achieve statistical significance); and an increase in total cholesterol in the 2000 ppm male group. Organ weight effects achieving statistical significance included: increased absolute pituitary weight at 6 months in the 2000 ppm male group and at 24 months in the 400 ppm and 2000 ppm male groups; increased absolute thyroid weight at 24 months in the 400 ppm male group (note: an increased absolute value for the 2000 ppm male group at 24 months was due to two tumorous organs); increased absolute left kidney weight at 24 months in the 2000 ppm male group; and increased absolute brain weight at 12 months in the 400 ppm and 2000 ppm female groups and at 24 months in the 2000 ppm male group (note: no pituitary or thyroid weights were reported for the groups sacrificed at 12 months, for reasons not explained). Histological findings achieving statistical significance for the main groups included: increased incidence of hemorrhage in the liver in the 2000 ppm male group; increased incidence of hemorrhage in the heart in the 2000 ppm male group; increased incidence of hyperplasia of the pancreatic islet cells in the 400 ppm and 2000 ppm male groups; and increased incidence of

calcification in the testis (tunica albuginea, vascular walls, convoluted deferent canal) in the 400 ppm and 2000 ppm male groups. The fact that the 0 ppm male group exhibited an unusually high rate of circulatory system tumors (18%) was not addressed in the report. Using the histology data from a blind reevaluation of liver sections (record 055398), the following were indicated (Fisher exact test, based on mice that were alive for  $\geq 1$  year): a dose-response increase in the incidence of nodular hyperplasia in the females (0 ppm, 1/50; 100 ppm, 5/49; 400 ppm, 7/48 [ $p=0.026$ ]; 2000 ppm, 10/50 [ $p=0.004$ ]); an increased incidence of nodular hyperplasia in the 400 ppm male group (0 ppm, 12/49; 400 ppm, 21/49 [ $p=0.043$ ]); and an increased incidence of the combination adenoma or carcinoma for the 2000 ppm male group (0 ppm, 13/49; 2000 ppm, 22/49 [ $p=0.046$ ]). **NOAEL = 100 ppm (in the 400 ppm males: increased incidences of hyperplasia of the pancreatic islet cells, calcification in the testis and hepatocellular nodular hyperplasia; increased specific gravity of the urine; increased prothrombin time; and increased absolute pituitary weight and thyroid weight; in the 400 ppm females: increased incidence of hepatocellular nodular hyperplasia and increased absolute brain weight).** In order to revisit the liver adenoma/carcinoma data, a time-to-tumor statistical analysis will need to be submitted. This study is **ACCEPTABLE. No rereview worksheet.** (Rinkus, 3/28/96). [Original review by C. Aldous, 6/18/86. Reviews of additional data on 3/17/87 and 3/24/87. See also memo, J. Carlisle to L. Nelson, (3/17/87). Original review Filename = Bentmoo1.220. Review of additional data by C. Aldous, 3/25/87, in file 220MOO1.BEN.]

355-042 043272 This record contains: the individual histological data for record 043271; and a table that lists on an individual basis the type and time of death, the initial and final bodyweight, and most gross pathology and histological findings for record 043271. **No worksheet.** (Rinkus, 3/28/96).

355-042 042992 "Studies on the 24-month oral chronic toxicity and potential carcinogenicity of Bentazon Reg. No. 51 929 (ZNT No. 81/273) in mice." (K. Takehara [study director]; Nippon Institute for Biological Science, Tokyo, Japan; no report identifier or report date on record 042992). This record appears to be basically the same as the "files 1 and 2" (the text and summary tables, respectively) of record 043271. Why it was submitted was not stated. However, it is not an exact duplicate of the corresponding pages in record 043271. For example, some female water intake tables have not been photocopied properly; some Japanese writing appears in the indices; and there appears to be mistaken entries (omissions) in the histological data concerning nonneoplastic lesions in the 400 ppm and 2000 ppm female mice that did not survive till the end of the study. In the rereview, it was assumed that the data in record 042992 were superseded by the data in record 043271. **No worksheet.** (Rinkus, 3/28/96).

355-042 042994 "Review of the studies on the 24 months oral chronic toxicity and potential carcinogenicity of Bentazon Reg. No. 51 929 (ZNT No. 81/273) in mice." (W.H. Butler; British Industrial Biological Research Association; no report identifier; the report is addressed to Dr. Drescher of BASF; date of review: April 9-12, 1985). This record contains individual histological data from a limited reevaluation of liver, lung (looking for metastasis from the liver), and testes sections from record 043271. Dr. Butler, who did the reread as a consultant to the Registrant, concluded the following: biliary proliferation and inflammatory infiltrate were prominent in many livers; autolysis was a confounding factor in distinguishing hepatocellular carcinoma from adenoma in the 2000 ppm male group; the incidence of hepatocellular carcinoma was not increased by treatments in either sex; the incidence of "simple nodules" in the liver for the 2000 ppm female group was increased; the extent of the calcification in the limited number of testes that were examined was slight; and the apparent dose-response in this testicular finding should be disregarded given that this lesion is a common effect in ageing mice. In the rereview, the histological data from the "blind" reevaluation involving three pathologists (record 055398) were used in lieu of the data in record 042994. **No worksheet.** (Rinkus, 3/28/96).

355-042 043260 "Supplemental report of the studies on the 24-month chronic toxicity of Bentazon

Reg. No. 51 929 (ZNT No. 81/273) in mice." (Takehara, K and Kudow, S.; Nippon Institute for Biological Science; no report identifier; the report is addressed to Dr. Butler and BASF; report dated Dec. 23, 1985). This record contains tables listing the histological determinations made for livers from both sexes in record 043271, which was based on the classification scheme of Squire and Levitt (Cancer Res. 35:3214-3223, 1975) vis-a-vis their reevaluations using the classification scheme of Vesselinovith et al. (Cancer Res. 38:2003-2010, 1978). The authors concluded that there was no significant difference in the incidences of noncarcinomatous nodules and carcinomas between the control and any of the treated groups, except noncarcinomatous nodules in the 2000 ppm female group, which was statistically increased. That the reevaluation resulted in two neoplastic nodules in the 0 ppm male group being reclassified as carcinomas while three, two and 11 carcinomas in the 100 ppm, 400 ppm and 2000 ppm male groups, respectively, were downgraded from carcinomas to noncarcinomatous nodules should be noted. In the rereview, the histological data from the "blind" reevaluation involving three pathologists (record 055398) were used in lieu of the data in record 043260. **No worksheet.** (Rinkus, 3/28/96).

059:055398 Mouse Oncogenicity (832) "Review of hepatic and pulmonary tissues of 24-month chronic oral toxicity study of bentazon Reg. No. 51 929 (ZNT No. 81/273) in mice". [Follow-up of final report of mouse study 041/042: Record #043272, etc. ]. Additional data: "blind" reexamination of mouse liver and lung slides by three pathologists. Results: No increase in incidence of male hepatocellular carcinomas; possible increase in hepatocellular adenomas in 2000 ppm males (apparent positive dose trend); confirmation of increased female hepatocellular nodular hyperplasia in (at least) 2000 ppm group; no further concern about possible increase in female bronchoalveolar tumors (rereading confirms not significant increase). C. Aldous, 3/17/87 (This data has been combined with concurrently submitted supplementary information in file 220MOO1.BEN, 3/25/87).

030 970027 Invalid Cannon Labs study. No useful data.

## REPRODUCTION, RAT

**\*\*355-066 073505** "Report on the Two-Generation Reproduction Study with Bentazon Technical (ZST-no. 86/48) in the Rat" (Suter, P. et al.; RCC Research and Consulting Company AG; RCC project no. 067757; March 9, 1989). Bentazon (not the sodium salt), 98% purity, was administered in the feed at concentrations of 0, 200, 800 and 3200 ppm. F0 adults and F1 adults were exposed for 70 days and 123 days, respectively, before their mating trial; and they were exposed for 113-132 days and 166-183 days, respectively, before they were sacrificed. Premating bodyweights were statistically reduced only in the F1 adults in the 3200 ppm groups (both sexes). Reduced bodyweight during gestation and (or) lactation was noted with the F0 and F1 females in the 3200 ppm groups. **Parental NOAEL = 800 ppm.** Reproductive indices pertaining to mating, fertility, fecundity and gestation were not affected by treatments in either mating trial. **Reproductive NOAEL =  $\geq$  3200 ppm.** The only progeny effect that was seen was reduced pup bodyweight in the 800 ppm and 3200 ppm groups for both generations; the reductions were evident starting day 1 (F1a pups) or day 4 (F2a pups) postpartum and were still present at weaning (day 21 postpartum). **Progeny NOAEL = 200 ppm.** This study is considered **ACCEPTABLE** even though several deficiencies were noted (discussed in worksheet W073505.834). (Rinkus, 11/28/95).

026 970025 [Tab: Report C5"] Laboratorium fuer Pharmakologie und Toxikologie, 4/12/76. Title: "Chronic oral toxicity of Bentazon in a reproduction study covering three generations of Sprague-Dawley rats". Bentazon, tech. 0, 20, 60, and 180 ppm in diet. NOEL = 180 ppm (HDT, no toxicity). Not acceptable nor upgradable. Dosages too low. Original review by A. Apostolou, 6/18/85. Not on disk.



## TERATOLOGY, RAT

**Note:** The acceptable study below, 054:055187, confirms conclusions from earlier studies that developmental toxicity is observed at levels at which significant evidence of maternal toxicity is not seen.

**\*\*054 055187** "Embryotoxicity (including Teratogenicity) Study with Bentazon Technical in the Rat, Project 064530". RCC, 1-21-87. Bentazon Technical (Lot N 187, 97.8%) administered by gavage to groups of 25 mated rats at dose levels of 0, 40, 100 or 250 mg/kg on days 6 - 15 of gestation. Maternal toxicity NOEL > 250 mg/kg/day. Developmental toxicity NOEL = 100 mg/kg/day (increased incidence of resorptions, decreased fetal weight, increased incidence of delayed skeletal ossification at 250 mg/kg/day). Acceptable, possible adverse effect since the developmental NOEL is less than the maternal NOEL. J. Parker, 3-24-87 (FILE 1B:220RTT1.JAP)

055 055188 "Dose-finding Embryotoxicity (including Teratogenicity) Study with Bentazon Technical in the Rat, Project 069772, First Study". Research and Consulting Company (RCC), Switzerland, 6-30-86. Bentazon Technical (Lot N. 187, 97.8%) was administered by gavage to groups of 5 mated rats at 0, 400, 600 or 800 mg/kg on days 6 - 15 of gestation. Death was noted in 2/5 females at 800 mg/kg and total resorption of all implantations was noted in all Bentazon treated groups. Decreased body weight gain was noted in all Bentazon treated groups. JAP 3-23-87 (1-liner from background section of review of study, 054:055187, above).

055 055189 "Dose-finding Embryotoxicity (including Teratogenicity) Study with Bentazon Technical in the Rat, Project 071897, Second Study". RCC, 8-5-86. Bentazon Technical (Lot N. 187, 97.8%) was administered by gavage to groups of 5 mated rats at 0, 100, 200 or 300 mg/kg on days 6 - 15 of gestation. Slightly reduced body weight gain was noted at 200 and 300 mg/kg/day. There was no other sign of maternal toxicity. Resorptions were increased and live litter size and weight were reduced at 300 mg/kg/day. There was a slight reduction in fetal weight at 200 mg/kg/day. Based on this range finding study, doses of 40, 100 and 250 mg/kg/day were selected for the full study. This appears to be a reasonable dose selection. JAP 3-23-87 (1-liner from background section of review of study, 054:055187, above).

040 43002 Nippon Institute for Biological Science, May, 1982. Title: "Teratogenicity study of Bentazon, Reg. No. 51 929 (ZNT No. 81/273), in rats by dietary administration". Bentazon, tech. 0, 2000, 4000 and 8000 ppm in diet over full gestation period. Maternal toxicity NOEL = developmental toxicity NOEL = 4000 ppm (8000 ppm dams with reduced body weight gain, hematuria, signs of depression, etc. Fetuses of 8000 ppm dams frequently runted, slight delayed ossification, and occasional liver hemorrhages and subcutaneous edema may be treatment related). Not complete as written. Upgradable. More information requested, including additional individual data. C. Aldous June 25, 1986 Filename = Bentrtt1.220

**Note: As of BASF letter dated 3/5/87, registrant does not plan to upgrade this study, as another rat teratogenicity study (054:055187) has been submitted in acceptable conformance with current EPA guidelines.**

**026 970028**, Medicinal-Biological Research Lab, 10/8/71. Title: "Study on possible teratogenic effect of 3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide on the rat following oral administration". Bentazon, tech. 0, 22, 67, and 200 mg/kg/day. No reported maternal toxicity. Developmental toxicity NOEL = 67 mg/kg/day: Substantial resorptions in 200 mg/kg/day group (66% of implantations, primarily late resorptions), frequent runting, anasarca, and misshapen bones in extremities, including radius and ulna, also tibia and fibula (possible adverse effect). Not acceptable, not upgradable: Numerous cases of spina bifida in vehicle controls, dosage levels not justified, unacceptable numbers of late fetal deaths reduced numbers of fetuses too much for teratogenicity to be properly evaluated. A. Apostolou, 6/18/85. Not on disk.

## TERATOLOGY, RABBIT

**\*\* 056 055191** "Embryotoxicity (including Teratogenicity) Study with Bentazon Technical in the Rabbit, RCC Project 064528", Research and Consulting Company (RCC), Switzerland, 1-26-87. Groups of 16 mated Chinchilla rabbits were treated by gavage on days 6 - 18 of gestation at dose levels of 0, 75, 150 or 375 mg/kg/day. Maternal toxicity NOEL > 375 mg/kg/day (HDT). Developmental toxicity NOEL = 375 mg/kg/day (increased resorption rate noted at 450 mg/kg/day in pilot study in absence of maternal toxicity). Acceptable with pilot study 057 055192, possible adverse effect. Parker, 3-25-87.

057 055192 "Dose-finding Embryotoxicity (including Teratogenicity) Study with Bentazon Technical in the Rabbit, RCC Project 064517", 10-16-86. Groups of 3 mated Chinchilla rabbits were treated by gavage on days 6 - 18 of gestation at dose levels of 0, 150, 300 or 450 mg/kg/day. Maternal toxicity NOEL > 450 mg/kg/day. Developmental toxicity NOEL = 150-300 mg/kg/day (increased resorption rate at 450 and possibly 300 mg/kg/day). This study was used by the laboratory to justify dose selection for the full scale teratology study, 056 055191. Parker, 3-25-87.

055 055190 "Study to determine the prenatal toxicity of 3-(1-methylethyl)-1H-2,1,3 -benzothiazin-4(3H)-on-2,2-dioxide in rabbits", BASF Department Toxicology, 3-6-78. Groups of 15 inseminated Himalayan rabbits were treated by gavage on days 6 - 18 of gestation with 0, 0, 50, 100 or 150 mg/kg/day. Dose level selection was too low and no toxicity was observed in any parameter measured. **Unacceptable, not upgradeable, no adverse effect indicated.** This study has been replaced, 056 055191. Parker, 3-26-87.

## GENE MUTATION

**\*\*039:43261 Salmonella** (1983, BASF Toxicology), Bentazon, 96.7%; 5 strains - TA1535, TA1537, TA1538, TA98 and TA100;  $\pm$  Sprague-Dawley rat liver S9 activation at 0, 20, 100, 500, 2500 or 5000 Fg/plate; two trials, 4/conc. in trial 1, 2 in trial 2; Negative for increased reversion rate. Acceptable. J. Gee, 6/9/86.

**\*\*039:43262 Salmonella** (1983, BASF Toxicology) Bentazon, 92.6%; TA1535, TA1537, TA1538, TA98 and TA100;  $\pm$  B6C3F1 male mouse liver activation at 0, 20, 100, 500, 2500 or 5000 Fg/plate; also, E. coli WP2uvrA; Repeat trials; no increased reversion rate; some cytotoxicity at 5000Fg/plate. Complete, acceptable J. Gee, 6/9/86.

039:43268 Salmonella (1985, BASF Toxicology) Title: "Report on the study of Bentazon-Na (pure active ingredient) and Bentazon-Na (technical grade) in the Ames test" (RZ Report No. 85/081). Bentazon "pure active" (99.5% pure Bentazon-Na) and "technical" grade (more accurately termed the MUP, 47.7% Bentazon-Na equivalent).  $\pm$  rat liver activation at 0, 500, 1000, 2500, 5000, 7500 or 10000 Fg/plate, TA1535, TA1537, TA1538, TA98, and TA100; repeat trials; Acceptable Supplementary Information (valid study, however technical grade of active ingredient was not used). No increase in reversion rates. J. Gee, 6/11/86, no file on disk. (1-liner updated 3/23/87 by C. Aldous, based on 3/5/87 rebuttal information).

039:43269 Salmonella (1976, Institute of Environ. Toxicol.) Title: "Mutagenicity testing on Bentazon in microbial systems". Bentazon, 94%; TA1535, TA1537, TA1538, TA98, TA100 and E. coli WP2 hcr;  $\pm$  rat liver activation at 0, 10, 50, 100, 500 or 1000 Fg/plate, 1 trial; NO increase in reversion rate reported - also did host-mediated in male mice. Unacceptable (no repeat, other deficiencies) J. Gee,

6/11/86, review not on disk.

039 43263 CHO/HGPRT (1985, BASF) Title: "Report on a point mutation test carried out on CHO cells (HGPRT locus) with the test substance Bentazon", RZ Report No 85/396. Bentazon, 93.9%;  $\pm$ mouse (B6C3F1) and rat (Sprague-Dawley) liver activation at 0, 0.1, 0.464, 1.0 or 4.64 mg/ml for 4 hours, 9-day expression; Increase in "uncorrected" mutation rate with mouse activation in 2 trials; negative with rat or -S9; Incomplete, unacceptable. No cytotoxicity data for final plating, mutation rate reported only on "uncorrected" basis. See discussion following report of study 039:43264. J. Gee, 6/9/86, review not on disk.

\*\*039 43264 CHO/HGPRT (1985, Litton Bionetics). Title: "Mutagenicity evaluation of Bentazon technical. 84/140 in the CHO HGPRT forward mutation assay". Bentazon, 93.9%;  $\pm$ rat and mouse liver activation at 0, 1.25, 2.5, 5, 7.5, 10, 12.5 or 15 mg/ml in repeat trials; no adverse effect identified; Complete, acceptable J. Gee, 6/9/86, Review not on disk.

Study 039:43264 used the same range of concentrations as 039:43263, and provides sufficient data to determine that the occasional statistically significant values are not of biological significance, but are due to scatter of some values for cloning efficiency and mutant colony counts. The calculated (mutation frequency)/ $10^6$  survivors reflects these. No dose-related response is noted and a number of high mutation frequency values occur at extreme cytotoxicity where other factors become important. Report 039:43264 mentions that a precipitate formed at  $\geq 0.156$  mg/ml, which was dissolved upon neutralization with NaOH, while the other one does not mention it up to 4.64 mg/ml. Since report 039:43263 is deficient in details, it is unknown whether they found the same problems. Without a complete report for 039:43263, the best judgment is that bentazon is not significantly mutagenic in CHO.

Comparison of the two tests:

	BASF	Litton
Cells	CHO-K1	CHO-K1-BH4
Test article	yellowish white	light brown
Purity	93.9%	93.9%
Lot	N169	84/140 technical
Treatment	4 hrs -FBS	4 hrs +FBS
Expression time	9 days	7 days
Medium	F12	F10
Select	6-TG, 10 FM (1.67 Fg/ml)	6-TG, 10 Fg/ml
Cell number	$3 \times 10^5/80 \text{ Cm}^2$	$2 \times 10^5/78 \text{ Cm}^2$
Number of plates	5	12

### CHROMOSOME EFFECTS

\*\*039 43267 Mouse micronucleus (1985, BASF) JG, 6/10/86. Bentazon 95.6%; 5/sex/group were exposed by oral gavage to 0, 200, 400, or 800 mg/kg, single dose, sacrificed at 16, 24 or 48 hours; No evidence of micronuclei formation; Acceptable : (Unacceptable in original review. Upgraded on basis of additional data in Doc. #355-053, pp. 16-17, and 057:55193. See Suppl. Info. review by J. Gee, 3/25/87 (not on disk)).

026 970030 (Tab Report C8) Title: "To assess the effect of oral administration of Bentazon on the fertility of male Sprague-Dawley rats with particular reference to dominant lethal factors". Rat dominant lethal (1971, Prof. F. Leuschner). Technical bentazon administered in diet to males at 0,

20, 60, and 180 ppm for a minimum of 13 weeks prior to mating with untreated females. No evidence of dominant lethal effects. Study **not acceptable or upgradeable**: doses far below an acceptable MTD for a dominant lethal study. A. Apostolou, 6/18/85, review not on disk.

026 970031 Mouse dominant lethal (BASF, 6/13/73) Title: "Report on the testing of 3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide for mutagenicity after intraperitoneal administration to the male mouse". Technical bentazon (no purity stated) administered once ip to males at 195 mg/kg (20% of LD<sub>50</sub>). No evidence of dominant lethal effect over 8 weeks of mating with untreated females. Study **not acceptable or upgradable**: dose was well below the maximum which could have been given, hence inadequate sensitivity. A. Apostolou, 6/18/85, review not on disk.

### DNA DAMAGE

\*\*039 43265 Mouse hepatocyte UDS in vitro (Feb., 1985, Litton Bionetics). Title: "Report on the evaluation of Bentazon in the in vitro mouse primary hepatocyte unscheduled DNA synthesis assay". Bentazon (free acid) purity = 92.6%, batch N 169). Male mice hepatocytes exposed for 18 hours to 0, 2.5, 5.0, 10.0, 25.1, 50.2, 100, 251, 502 Fg/ml; No evidence of UDS up to 60% survival; Acceptable, complete. J. Gee, 6/10/86, Review not on disk. Update of this one-liner reflects additional data received in 3/5/87 submission by registrant. See review by C. Aldous, 3/23/87, file 220844A.BEN.

\*\*039 43266 In vivo mouse UDS. (1985, Litton Bionetics). Bentazon, (free acid) purity = 92.6%, batch N 169). 2 males/grp were given 0, ~41, ~90, ~180 or ~360 mg/kg i.p.; hepatocytes harvested 6 hours posttreatment; incorporation of <sup>3</sup>H-tdR for 18-19 hours; No evidence of UDS; Acceptable (Original review by J. (Remsen) Gee, 6/10/86. Upgraded from unacceptable status on receipt of additional information in Document #355-053, p. 21 and data in 057:55195. See Suppl. Info. form by J. Gee, 3/25/87.)

039 43270 B. subtilis rec assay (1976, Institute of Environ. Toxicol.) Title: "Mutagenicity testing on Bentazon in microbial systems (rec-assay - Bacillus subtilis"). Bentazon, 94%; H17 & M45; 0, 20, 100, 200, 500, 1000 or 2000 Fg/10mm disk; No difference in growth; no activation. Unacceptable, 1 value/treatment only. J. Gee, 6/11/86, review not on disk.

### NEUROTOXICITY

Not required at this time.

**NOTE:** All studies received by the DPR Medical Toxicology Branch up to 9/30/99 have been considered in this SUMMARY OF TOXICOLOGY DATA.