# Bentazon (Basagran); CASRN 25057-89-0

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Bentazon (Basagran)

**File First On-Line 03/03/1987**

| Category (section) | Assessment Available? | Last Revised |
|---|---|---|
| **Oral RfD (I.A.)** | yes | 03/02/1998 |
| **Inhalation RfC (I.B.)** | message | 03/02/1998 |
| **Carcinogenicity Assessment (II.)** | yes | 03/02/1998 |

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is

essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

### I.A.1. Oral RfD Summary

| Critical Effect | Experimental Doses* | UF | MF | RfD |
|---|---|---|---|---|
| | NOAEL: 3.2 mg/kg bwt/day | 100 | 1 | 3.0 E-2 mg/kg/day |
| **Confidence -- Medium**<br><br>**Note: 0.032 is rounded down to 0.03 mg/kg bwt/day** | | | | |
| **(1) Blood loss into the gastrointestinal tract** | NOAEL<br>Reported - 3.2 mg/kg bwt/day<br>Adjusted - 3.2 mg/kg bwt/day | | | |
| **(2) Coagulation defect in male and female dogs.** | LOAEL<br>Reported - 13.1 mg/kg bwt/day<br>Adjusted - 13.1 mg/kg bwt/day | | | |
| **Study Type - 1 year dog feeling study - reference -- Allen et al., 1989** | | | | |
| **Dose-related increase in red areas (presumed blood) in feces, coagulation defect** | Defined Dose Levels:<br><br>NOAEL --- 100 ppm<br>NOAEL --- (ADJ) -- 3.2 mg/kg bwt/day<br>LOAEL --- 400 ppm<br>LOAEL --- (ADJ) -- 13.1 mg/kg bwt/day | | | |

*Conversion Factors: none

## I.A.2. Principal and Supporting Studies (Oral RfD)

Allen et al., 1989. 52-week oral toxicity (feeding) study with bentazon technical (ZST No. 86/48) in the dog. Amendment (MRID No. 410549-01, 41123001, HED Doc. No. 008079). Unpublished study prepared by RCC Research and Consulting Co. AG. Available from US EPA. Write to Freedom of Information Office , US Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460.

Groups of beagle dogs (6/sex/dose) were fed diets containing 0, 100, 400, or 1,600 ppm (average intake of test material: 0, 3.2, 13.1, and 52.3 mg/kg bwt/day) bentazon technical for 1 year. Animals received 300 g of repelleted standard Kliba No. 335 dog maintenance feed for 3 h daily and water was provided ad libitum.

Body weight gains for the test animals were compared by means of t-tests for various periods of dosing. The mean percent body weight gains were slightly decreased at 400 ppm compared to controls, but no statistically significant differences in percent body weight gain were found (i.e., $p < 0.05$) for any period of dosing at 400 ppm.

Clinical signs were mostly limited to the high-dose group (1,600 ppm); there was a suggestive dose-related increase in the incidence of males with feces containing red areas (none at 0 and 100 ppm, 1/6 at 400 ppm, and 2/6 at 1,600 ppm); however, the frequency of the occurrences was not provided. Although the animal incidences of 1/6 (16.6%) at the mid-dose level and 2/6 (33.3%) at the high-dose level versus 0% in the controls lack statistical significance (owing to the small number of animals), this dose-related effect is considered of biological significance when considered with the toxic effects of bentazon on blood coagulation in mice, rats, and another study in dogs (BASF AG, 1970). In male beagles, the partial thromboplastin time (PTT) was elevated ($p < 0.05$) at 1,600 ppm (49.7 mg/kg bwt/day). Therefore, in view of the dose-dependent presence of feces with red areas (though not chemically confirmed to be blood) in dogs fed bentazon at 400 ppm (13.3 mg/kg bwt/day) and 1,600 ppm (49.7 mg/kg bwt/day), and the absence of red areas in feces of animals at 0 and 100 ppm (3.2 mg/kg bwt/day), it is difficult to discount the presence of feces with red areas in mid-dose male dogs as not being treatment related. Therefore, the LOAEL of bentazon in beagle dogs should be established at 400 ppm (13.1 mg/kg bwt/day), based on possible adverse effects on blood coagulation or blood loss in the intestinal tract in male beagles. The NOAEL appears to be 100 ppm (3.2 mg/kg bwt/day).

From the studies provided, one can determine that the longer studies with lower dosages provide appropriate data with which to establish a dose-response relationship. The effect considered most critical in the studies provided was that of the derangement of the hemostasis mechanism because exposure resulted in a significant 40% reduction in hemoglobin, 30%

reduction in red blood cell counts, and 33% reduction in hematocrits compared to control group values in the shorter 13- week study at 75 mg/kg bwt/day. Several other effects were also considered in establishing the appropriate endpoint for an RfD and included the loss in body weight, the effects on the liver, and even the prostatitis noted in one of the earlier studies. Prostatitis in the subchronic, 90-day dog study occurred at 7.5 mg/kg bwt/day with an NOAEL of 2.5 mg/kg bwt/day, but is not considered to be a significant effect because the same effect was not found in a larger (6/sex/dose) and longer 1-year study that did not negate the LOAEL of 7.5 mg/kg bwt/day but raised the NOAEL with some degree of certainty because of the lack of effect seen at a slightly higher dosage (3.2 mg/kg bwt/day). However, the dose level associated with the clotting times and intestinal blood loss problems in the male dog was considered to be the most critical and provided the lowest and most supportable NOAEL in the data set.

### I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 100.

The uncertainty factor of 100 reflects a default factor of 10 for interspecies extrapolation and a similar default factor of 10 for intraspecies variability (Lehman and Fitzhugh, 1954).

MF = 1

Essentially a full database and adequately conducted studies were present and no additional modifying factors were added.

The further addition of modifying factors to provide added protection to the newborn or young who might be exposed to bentazon was not needed. This lack of need was due to several factors: the data on the newborn and young did not indicate that they were significantly more sensitive than the adults in the same study, toxicity to the development of the fetus and young was of a general growth toxicity, the NOAELs for the studies with data on the young were so much higher than the NOAEL in the chronic dog study, and the fact that dogs appeared to be somewhat more sensitive to the effects of bentazon than were rodents.

### I.A.4. Additional Studies/Comments (Oral RfD)

(1) 1-Year feeding -- dog. Principal study -- see previous description (Allen et al., 1989) (submitted to support registration).

(2) 2-Year feeding/carcinogenicity -- rat (Takehara and Tajima, 1984) (submitted to support registration).

Groups of Fischer 344/Du rats (70/sex/dose with a 6- and 12-month interim sacrifice of 10/sex/dose) were fed bentazon in the diet for 2 years at dose levels of 0, 200, 800, and 4,000 ppm (male: 0, 9, 35, and 180 mg/kg bwt/day; female: 0, 11, 45, and 244 mg/kg bwt/day). Dose selection was based on 1-month study in which rats were administered bentazon at dose levels of 5,000 and 10,000 ppm. Some of the rats receiving 10,000 ppm died showing hemorrhagic lesions. Animals fed 5,000 ppm developed hemorrhagic lesions in the urogenital organs.

Mean body weights of both high-dose males and females were significantly ($p < 0.05$) lower than controls, in general, from week 5 onward. In males receiving 800 ppm, body weights were significantly ($p < 0.05$) lower than controls for most weeks between weeks 19-36. In females receiving 800 ppm, mean body weights were significantly lower than control only on weeks 60 and 65. Compound-related reductions in food consumption were observed in mid- and high-dose males. No compound-related changes in food consumption were observed for female rats at any dose levels. Weekly mean water consumption was significantly ($p < 0.05$) increased in high-dose male and female rats throughout most the study. For mid-dose animals, mean water intake was sporadically increased in males and females.

For animals sacrificed at 24 mo, urinary specific gravity was lower in high-dose animals as compared to controls, but urine volume was either similar to or significantly ($p < 0.001$) less (in females) than controls.

Absolute and relative mean thyroid weights were significantly ($p < 0.05$) decreased at 6 and 12 mo in mid- and high-dose males. A dose-dependent decrease in absolute and relative mean thyroid weights was suggested by the data in females at 12 mo. However, only the absolute thyroid weight in the high-dose group was significantly ($p < 0.05$) reduced when compared to controls. No significant differences in thyroid weights were observed at 24 mo. Absolute liver and spleen weights were significantly ($p < 0.05$) decreased in high-dose males at 6, 12, and 24 mo. Relative weights were significantly decreased at 6 and 24 mo.

Mean platelet counts were significantly ($p < 0.01$) decreased in mid- and high-dose males and high-dose females at 6 mo. Prothrombin times (PT) and partial thromboplastin times (PTT) were significantly ($p < 0.01$) longer than control values in high-dose (4,000 ppm) males at 6, 12, and 24 mo. Prolonged PTTs were also observed at 12 mo in mid-dose males and females and high-dose females. These alterations in coagulation were considered to be compound related.

Based on the effects observed at the mid-dose, the NOAEL and LOAEL values for systemic toxicity appear to be 200 ppm (male: 9 mg/kg bwt/day; female: 11 mg/kg bwt/day) and 800 ppm (male: 35 mg/kg bwt/day; female: 45 mg/kg bwt/day), respectively.

(3) 2-Generation reproduction -- rat (Suter et al., 1989) (submitted in support of registration).

In a two-generation reproduction study, groups of Wistar/Han rats (25/sex/dose) were fed diets containing bentazon technical at dosage levels of 0, 200, 800, and 3,200 ppm (approximately 0, 15, 62, and 249 mg/kg bwt/day). Mean test material intake ranged from 15 to 238 and from 17 to 269 mg/kg bwt/day for F0 males and females, respectively, and from 14 to 227 and from 16 to 262 mg/kg bwt/day for F1 males and females, respectively, during the premating periods.

Weight losses in dams during the lactation periods of both generations show trends toward significant reductions at the highest dose level, though the weight loss was less than 10% of the control group values. Significantly decreased food consumption was observed in the F1 generation among high-dose females during the premating period and the beginning of the gestation period. A significant trend toward reduced food consumption was observed in the F1 generation during study days 1-8 and 22-29 and on gestation day 0-7.

In the F0 generation, increased incidences were seen in kidney mineralization (1/25 and 3/25 for control and high-dose males, respectively) and liver microgranuloma (7/25 and 16/25 for control and high-dose males, respectively). Also in the F1 generation high-dose males, increased incidences were seen in mineralization of the kidneys (1/25 and 6/25 for control and high-dose males, respectively). Because no historical control data were submitted, the relevance of these data cannot be determined.

No compound-related adverse effects were observed on fertility, implantation sites, postimplantation loss, and offspring survival. Statistically significant and probably biological significant reductions in pup weights and pup weight gains were observed at the high dose levels. Although primarily observed in the P generation at days 4 and 7 (10%-20%), pup weight gains were reduced throughout lactation (10%-19%) in the 3,200 ppm dose group of the F1 generation.

Based on reduced food consumption and histopathological findings among high-dose animals, the LOAEL for parental toxicity is 3,200 ppm (249 mg/kg bwt/day). The NOAEL for parental toxicity is 800 ppm (62 mg/kg bwt/day).

Based on reduced pup weights and pup weight gains, the LOAEL for reproductive toxicity is 800 ppm (62 mg/kg bwt/day). The NOAEL for reproductive toxicity appears to be 200 ppm (15 mg/kg bwt/day).

(4) Developmental toxicity -- rat (Becker et al., 1986a) (submitted in support of registration).

In a dose-ranging study, oral administration of technical bentazon (0, 100, 200, and 300 mg/kg bwt/day) to rats during days 6-15 of pregnancy did not result in any increase in mortality, observable clinical changes, or gross pathology among the treated groups as compared to controls. There was no consistent, compound-related effect on maternal body weight or food consumption. At the highest dose tested there was an increase in percent of embryonic and fetal absorption over control values (primarily fetal in nature), with surviving fetal body weights generally lower than body weights of controls. Based on the findings in this study, dose levels were established in the full developmental toxicity study.

In the main developmental toxicity study, oral administration of technical bentazon at dosage levels of 0, 40, 100, and 250 mg/kg bwt/day to pregnant Wistar rats during days 6-15 of gestation did not produce any consistent signs of systemic maternal toxicity such as clinical signs or symptoms, mortality, changes in mean body weight, or decreases in food consumption. Based on these findings, the NOAEL for maternal toxicity is greater than or equal to 250 mg/kg bwt/day.

At the highest dose tested, bentazon produced an increase in postimplantation loss (fetal resorptions, but no increase in embryonic resorptions). This was accompanied by a depression in the body weights of those fetuses surviving until day 21 sacrifice. It also produced an effect on the rate of growth, as evidenced by a decrease in the rate of ossification in the phalangeal nuclei of fore and hind limb digits, the 5th sternebra, and cervical vertebra. A decrease in body weight in conjunction with delays in tissue maturation suggests that bentazon is a general fetal systemic toxicant. Based the above effects, the LOAEL for developmental toxicity is 250 mg/kg bwt/day. The NOAEL for developmental toxicity appears to be 100 mg/kg bwt/day.

(5) Developmental toxicity -- rabbit (Becker et al., 1986b) (submitted in support of registration).

In a dose-ranging study, Chinchilla rabbits (3/dose group) were administered technical bentazon by gavage daily at dose levels of 0, 150, 300, and 450 mg/kg bwt/day) from day 6-18 of post coitus.

Two of three does were pregnant in all dose groups. The high-dose group had one doe in which no live fetuses were observed, only embryonic resorptions. The mean body weights of pregnant does in the 300 mg/kg bwt/day dose group were initially lower (because of one low-weight rabbit) than other dose groups and remained depressed during the study. Based on differences in mean body weight gains (%), there does not appear to be any compound-related effect on weight gain. However, the lack of an adequate number of pregnant does makes these comments quite tentative in nature. Food consumption data have the same limitations as for body weight gain, with the additional factor that one of the control rabbits had spillage of food

during day periods of 15-19, 19-24, and 24-28.

Preimplantation losses (%) were higher in the high-dose group as compared to the controls (20% vs. 0%). The mean number of fetuses/litter decreased in the high-dose group as compared to the control or other treatment groups (7.5, 8.5, 8.0, and 2.0 for the control, low-, mid-, and high-dose groups, respectively).

Mean fetal weights (g) appeared to be lower in all treated groups as compared to the controls (40.3, 31.5, 34.2, and 32.3 for the control, low-, mid-, and high-dose groups, respectively). The study authors noted that this difference is an artifact of the high mean body weight of the control fetuses because historical control weights (34.6 g/vehicle control animals, 33.4 g/untreated control animals) were similar to the treated groups.

It is concluded that bentazon produced a significant increase in embryonic resorptions at the highest dose tested (450 mg/kg bwt/day) as compared to the control group. Mean body weight and food consumption data were inadequate to permit a dose-related systemic toxicity response to be determined.

In the main developmental toxicity study, oral administration of technical bentazon at dosages of 0, 75, 150, and 375 mg/kg bwt/day to female Chinchilla rabbits during the period of major organogenesis (days 6-18) did not produce any appreciable evidence of compound-related maternal toxicity as measured by changes in mean body weight, mean body weight gains, corrected body weight gain, food consumption, or overt clinical signs except for the observation of one doe with a partial abortion, embryonic resorptions, and no living fetuses. This observation is probably compound related because 2/3 does treated with bentazon during the dose-ranging study at a higher dose (450 mg/kg/day) produced almost complete resorption of the observed embryos. Therefore, the LOAEL for maternal toxicity was set at 375 mg/kg bwt/day. The NOAEL for maternal toxicity appears to be 150 mg/kg bwt/day.

There were no significant effects of bentazon administration on mean resorptions/doe, mean numbers of liver fetuses/doe, mean fetal weights, or mean sex ratios in those animals fully evaluated at day 29 of sacrifice. No abnormal developmental toxicity was observed at any dose level for gross, visceral, or skeletal findings. The developmental NOAEL appears to be 375 mg/kg bwt/day.

Other Data Reviewed:

(6) 13-week feeding -- dog (BASF AG, 1970) (submitted in support of registration).

Groups of beagle dogs (3/sex/dose) were administered bentazon orally for 13 weeks at dose

levels of 0, 100, 300, 1,000, and 3,000 ppm (0, 2.5, 7.5, 25, and 75 mg/kg bwt/day).

Dogs receiving 3,000 ppm produced a variety of symptoms, and 1 of 3 males and 2 of 3 females at that dose died during the 13 weeks of the study. Dogs tended to be sedated, eventually lost weight, became cachectic, developed diarrhea, frequently vomited, had skin lesions, stomatitis, conjunctivitis, and the general appearance of severely compromised health. The 3 males at 3,000 ppm exhibited fresh blood in their stools by the end of the study. Several urinalysis, hematological, and blood chemistry tests confirmed the picture of general ill health. In particular, the blood chemistry tests suggested pathology of the liver, and this effect was borne out by daily observations, gross pathology (e.g., weight loss, cachexia, stomatitis, and other areas of inflammation and sores on skin and surface membranes), and microscopic inspection (e.g., fatty infiltration of heart and liver, necrotic congestion of the liver, albuminous swelling of the kidneys, etc.). Prostatitis was observed in all three 3,000 ppm males, in 1 of 3 males in the 1,000 ppm group, and one 300 ppm male. One of the three 3,000 ppm males and one 1,000 ppm male had empty epididymal ducts. Only the latter animal had positive signs of epididymal maturation deficiency. On the basis of observed prostatitis, a provisional LOAEL of 300 ppm (7.5 mg/kg bwt/day) can be established, with the associated NOAEL appearing to be 100 ppm (2.5 mg/kg bwt/day).

(7) 13-week feeding -- rat (Tennekes et al., 1987) (submitted in support of registration).

Groups of Wistar rats (10/sex/dose) were administered bentazon in diet for 13 weeks at dose levels of 0, 400, 1,200, and 3,600 ppm (male: 0, 25.3, 77.8, and 243.3 mg/kg bwt/day; female: 0, 28.9, 86.1, and 258.3 mg/kg bwt/day). An additional 10 animals/sex were placed in the control and high-dose groups and used for a 28-day recovery group.

Three deaths (1 male and 2 females) occurred in the high-dose group during the course of the study. Female but not male body weights were significantly depressed as compared to controls in the high-dose group, with the mean weights remaining somewhat lower in the recovery period. Males had a minimal but consistent increase in food consumption. Bentazon appears to produce an inconsistent effect (between sexes) upon thromboplastin time (PT) and prothrombin time (PTT) in the high-dose groups as compared to controls, with males having a statistically significant increase in these parameters and females having a significant depression (PT only). These values returned to control levels in the recovery period. Reversible changes in clinical chemistries were observed in male and female rats during compound administration and recovery. No statistically significant increases in histopathological changes were observed. However, in the females there is a suggestion of an increase in lung thrombi and dilation of the uterine horns in the high-dose group as compared to controls.

Based on the effects observed at the highest dose tested, the LOAEL for systemic toxicity is 3,600 ppm (male: 243.3 mg/kg bwt/day; female: 258.3 mg/kg bwt/day). The NOAEL for systemic toxicity appears to be 1,200 ppm (male: 77.8 mg/kg bwt/day; female: 86.1 mg/kg bwt/day).

Data Gaps: None

***For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF)***.

### I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

The study design of the principal study was adequate and complete. However, data on test material stability analysis could not be verified, there was a possibility that unthrifty animals were used, and the presence of blood in the feces was not chemically proven. Therefore, the principal study is given a medium confidence rating. The database is given a high confidence rating because there are no data gaps and additional studies support the principal study. The use of a medium confidence in the principal study and a high confidence in the database supports a medium-to-high confidence in the RfD.

***For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)***.

### I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is presented in the Toxicological Review of Bentazon (CAS No. 25057-89-0). (EPA, 1998)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to US EPA, 1998, Toxicological Review of Bentazon. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — None

Agency Consensus Date — 10/20/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Bentazon (Basagran) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

### I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

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## I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

### I.B.6. EPA Documentation and Review of the Inhalation RfC

No data available with which to establish an RfC value for bentazon.

Other EPA Documentation — None

Agency Consensus Date — 10/20/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Bentazon (Basagran) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

### I.B.7. EPA Contacts (Inhalation RfC)

N.A.

# II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimated in terms of either risk per µg/L drinking water or risk per $\mu g/m^3$ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

## II.A. Evidence for Human Carcinogenicity

### II.A.1. Weight-of-Evidence Characterization

Under EPA's 1986 Guidelines for Carcinogen Risk Assessment, Bentazon would be classified as *evidence of non-carcinogenicity for humans*, or a Group E chemical. Under EPA's proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996), Bentazon would be characterized as *not likely to be carcinogenic to humans by any route of exposure.* Additionally, the Health Effects Division, Office of Pesticide Programs cancer peer review committee has concluded after evaluating the known and submitted studies that the animal bioassays were essentially negative for a carcinogenic effect from chronic feeding, and under the older classification system the chemical was classed as an E for carcinogenic potential (U.S. EPA, 1992).

The metabolic pathways of bentazon and the handling of it by the mammalian system are well understood and do not produce any significant suspect reactive species. The mutagenicity studies do not indicate a mutagenicity hazard from the chemical and structure-activity comparisons to similar chemical structures are negative for significant effects regarding carcinogenic potential.

***For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).***

***For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).***

## II.A.2. Human Carcinogenicity Data

The Agency is unaware of any data available for review.

## II.A.3. Animal Carcinogenicity Data

Studies were considered adequate for evaluation of the carcinogenic potential in animals. The results were considered to not be indicative of a hazard to test animals.

1. Studies on the 24-month oral chronic toxicity and potential carcinogenicity of bentazon in rats. Core grade: guideline, (Takehara, et al. ,1984) (data submitted to support registration).

Groups of Fischer 344/Du rats (50/sex/dose with a 6 and 12 month interim sacrifice each containing an additional 10/sex/dose) were fed bentazon in the diet for 2 years at dose levels of 0, 200, 800, and 4000 ppm (Male: 0, 9, 35, and 180 mg/kg/day; Female: 0, 11, 45, and 244 mg/kg-day). Dose selection was based on a supplementary 1-month study in which rats were administered bentazon at dose levels of 5000 and 10,000 ppm. Some of the rats receiving 10,000 ppm died showing hemorrhagic lesions. Animals fed 5000 ppm developed hemorrhagic lesions in the urogenital organs.

Mean body weights of both (4000 ppm) high-dose males and females were significantly ($p < 0.05$) lower than controls, in general, commencing at week 5. In males receiving 800 ppm, body weights were significantly ($p < 0.05$) lower than controls for most weeks between weeks 19-36. Compound-related reductions in food consumption were also observed in mid- and high-dose males. No compound-related changes in food consumption were observed for female rats at any dose levels.

Absolute and relative mean thyroid weights were significantly ($p < 0.05$) decreased at 6 and 12 months in mid- and high-dose males. A dose-dependent decrease in absolute and relative mean thyroid weights was suggested by the data from females at 12 months. However, only the absolute thyroid weight in the high-dose group was significantly ($p < 0.05$) different from control. No significant differences in thyroid weights in the females were observed at 24 months. Absolute liver and spleen weights were significantly ($p < 0.05$) decreased in high-dose males at 6, 12 and 24 months and relative weights were significantly decreased at 6 and

24 months. There was little difference in longevity of the treated animals compared to controls.

Neoplastic findings in the animals which either died or were sacrificed *in extremis* and those that were sacrificed at termination of the study indicate that pheochromocytomas were significantly increased in females fed 4000 ppm of bentazon in the diet. There was an apparent dose-response with this finding. Further information on the historical incidence of this tumor in the testing laboratory indicated that the apparent increase was well within the 13% control values reported by the testing laboratory. Females in the 800 and 4000 ppm dosage groups exhibited a slight increase in endometrial polyps with 36% and 24% respectively when compared to a 20% incidence in controls. These incidence rates were not statistically significantly increased. Chromophobe adenomas were statistically significantly increased in the females only in the 200 ppm dosed group 18/29 (62%) when compared to 11/31 (35%) in controls. These incidences are not considered to be biologically significant due to the lack of a dose response at higher doses. This study has been judged to be negative for a carcinogenic response to the exposure in the diet of male and female rats.

Based on the effects observed at the mid-dose, the NOAEL and LOAEL for systemic toxicity are 200 ppm (Male: 9 mg/kg-day; Female: 11 mg/kg-day) and 800 ppm (Male: 35 mg/kg-day; Female: 45 mg/kg-day), respectively.

2. Studies on the 24-month oral chronic toxicity and potential carcinogenicity of bentazon, reg. No. 51 929 (ZNT No. 91/273), in mice. Core grade: Guideline. (Tajima, et al., 1984). (submitted in support of registration).

Bentazon was fed to male and female B6C3F1 mice at levels of 0, 100, 400, or 2000 ppm in the diets for 2 years. There were increased prothrombin times in males that received 400 or 2000 ppm. The increased clotting times were accompanied by an increase in hemorrhage in the liver and heart of the high dose males which died during the study. There was an increase in calcification of the tunica albuginea of the testes and an increase in islet cell hyperplasia of the pancreas in males receiving 400 or 2000 ppm of bentazon. There was a transient, slight decrease in mean body weights in males at intervals between weeks 7 and 23 and increases in organ weights of kidneys, thyroids and pituitaries in mid and high-dosed males. There were no effects on body weights from exposure to the chemical in dosed females. Increased liver weight and relative kidney weights were noted in mid-dose females.

Reports of three pathologists reading the histopathological slides of livers were evaluated as well as the historical control data for the liver tumors in the B6C3F1 mice. It was concluded that there was no real increase in the incidence of hepatocellular carcinomas and the chemical should be classified as a Group E (evidence of non-carcinogenicity for humans), based upon a

lack of evidence of carcinogenicity in two adequate animal species studied (U.S. EPA. 1992). It should be emphasized, however that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

### II.A.4. Supporting Data for Carcinogenicity

Mutagenicity:

Overall, the weight of the evidence does not suggest a significant mutagenicity concern for bentazon. Acceptable tests have been conducted in three categories: gene mutations, structural chromosome aberrations, and other genotoxic effects (DNA damage and repair) (U.S. EPA, 1991).

1. Bentazon was negative in reverse mutation assays with Salmonella strains (+S9) at doses of 20-5,000 ug/plate and in E. coli WP2 uvrA (+S9) at levels of 10-1,000 ug/plate (Engelhardt, 1985 a).

2. Bentazon was negative in the CHO/HGPRT forward mutation assays with and without rat liver S9 mix at concentrations of 100-5,000 ug/mL (DenBoer, 1985; Mullerschon, 1991).

3. In the mouse micronucleus test, bentazon did not cause a significant increase in micronuclei in NMRI mice of either sex at dosages between 200 and 800 mg/kg (Engelhardt, 1985 b).

4. Bentazon was negative for unscheduled DNA synthesis in an acceptable UDS/primary mouse hepatocyte assay at doses of 2.5 and 502 ug/mL (Cifone, 1985).

## II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

No data available.

## II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

No data available.

## II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

### II.D.1. EPA Documentation

Source Document — U.S. Environmental Protection Agency. (1998) Toxicological Review of Bentazon (CAS No. 25057-89-0).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to US EPA 1998, Toxicological Review of Bentazon. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

### II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 10/20/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Bentazon (Basagran) conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

### II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

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## III. [reserved]
## IV. [reserved]
## V. [reserved]

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# VI. Bibliography

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0

## VI.A. Oral RfD References

Allen, TR; Frei, TH; et al. (1989) 52-week oral toxicity (feeding) study with bentazon technical (ZST No. 86/48) in the dog. Amendment (MRID No. 410549-01, HED Doc. No. 008079). Unpublished study prepared by RCC Research and Consulting Co. AG.

BASF AG. (1970) Authors Zeller and Kirsch; 13-week toxicity of 3-isopropyl 2,1,3-benzothiadiaxinone-(4)-2,2-dioxide to beagles when administered with the food. MRID No. 00091058, HED Doc. No. 000394, 0003912. Unpublished study prepared by BASF AG.

Becker, HD; Frei, D; Vogel, W; et al. (1986a) Embryotoxicity (including teratogenicity) study with bentazon technical in the rat. Unpublished study (No. 87/5004) prepared by RCC Research and Consulting Co. AG.

Becker, H; Mueller, E; Vogel, W; et al. (1986b) Embryotoxicity (including teratogenicity) study with bentazon technical in the rabbit. (MRID No. 40114202, HED Doc. No. 006231). Unpublished study (No.87/5003) prepared by RCC Research and Consulting Co. AG.

Lehman, AJ; Fitzhugh, OG. (1954) 100-fold margin of safety. Assoc Food Drug Off US Q Bull 18:33-35.

Suter, P; et al. (1989) Report on the two-generation reproduction study with bentazon technical (ZST No. 86/48) in the rat. MRID No. 4100549-02, HED Doc. No. 008079.

Takehara, K; Tajima, M. (1984) Studies on the 24-month chronic toxicity of bentazon in rats. MRID No. 00142831, 00142833, 40871701, 40871702, HED Doc. No. 006459, 007247. Unpublished translation prepared by Nippon Institute for Biological Sciences.

Tennekes, H; Horst, K; Leutkemeier, H; et al. (1987) Report on the 13-week oral toxicity (feeding) study with bentazon technical in the rat. MRID No. 40222201, HED Doc. No. 006421. Unpublished study prepared by RCC Research and Consulting Co. AG.

U.S. Environmental Protection Agency (1998) Toxicological Review of Bentazon (CAS No. 25057-89-0) in Support of Summary Information on Integrated Risk Information System (IRIS). Available online at http://www.epa.gov/iris.

## VI.B. Inhalation RfC References

None

## VI.C. Carcinogenicity Assessment References

Cifone, M. (1985) Evaluation of bentazon in the in vitro mouse primary hepatocyte unscheduled DNA synthesis assay. Unpublished report prepared by Litton Bionetics.

DenBoer, W. (1985) Mutagenicity evaluation of bentazon technical (84-140) in the CHO/HGPRT forward mutation assay. Unpublished study prepared by Litton Bionetics, Inc.

Engelhardt, G. (1985 a) Report on the study of bentazon in the Ames Salmonella/microsome plate assay and reverse mutation assay - E. coli WP2 uvrA. Unpublished study prepared by BASF AG.

Engelhardt, G. (1985b) Cytogenetic investigations in NMRI mice after a single oral administration of bentazon: Micronucleus test. Unpublished study prepared by BASFAG.

Mullerschon, H. (1991) Gene mutation assay in Chinese Hamster Ovary Cells in vitro with bentazon. Unpublished study prepared by Cytotest Cell Research.

Tajima, M., K. Takehara, M. Itabashi, et al. (1984) Studies on the 24-month oral chronic toxicity and potential carcinogenicity of bentazon, reg. No. 51 929 (ZNT No. 91/273), in mice.

Takehara, K. and M. Tajima. (1984). Studies on the 24-month oral chronic toxicity and potential carcinogenicity of bentazon in rats.

U.S. Environmental Protection Agency. (1992) First and Second Peer Review of Bentazon. Memorandum from James Rowe, Alberto Protzel and George Ghali to Joanne Miller dated January 14, 1992.

U.S. Environmental Protection Agency (1996). Proposed Guidelines for Carcinogen Risk Assessment. Federal Register 61(79):17960-18011.

U.S. Environmental Protection Agency (1998) Toxicological Review of Bentazon in Support of Summary Information on Integrated Risk Information System (IRIS). Available online at http://www.epa.gov/iris.

## VII. Revision History

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

| Date | Section | Description |
|---|---|---|
| **03/02/1998** | I.A.,II.,VI. | New RfD, Cancer Assessment, RfC message |
| **10/28/2003** | I.A.6., I.B.6., II.D.2. | Screening-Level Literature Review Findings message has been added. |

## VIII. Synonyms

Substance Name — Bentazon (Basagran)
CASRN — 25057-89-0
Last Revised — 03/02/1998

- 25057-89-0
- BAS 351-H
- BASAGRAN
- BENDIOXIDE
- Bentazon
- BENTAZONE

- 1 H-2,1,3-BENZOTHIADIAZIN-4 (3H)-ONE-2,2-DIOXIDE, 3-ISOPROPYL-
- 3-ISOPROPYL-2,1,3-BENZOTHIADIAZINON-(4)-2,2-DIOXID
- 3-ISOPROPYL-1 H-2, 1-3-BENZOTHIADIAZIN-4(3H)-ONE-2,2-DIOXIDE
- 3-(1-METHYLETHYL)-1H-2,1,3-BENZOTHIAZAIN-4(3H)-ONE,2,2-DIOXIDE