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TOXICOLOGICAL REVIEW

of

BENTAZON

(CAS No. 25057-89-0)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

February 1998

U.S. Environmental Protection Agency
Washington, DC

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Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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FOREWORD

The purpose of this review is to provide scientific support and rationale for the hazard identification and dose-response information in IRIS pertaining to chronic exposure to bentazon. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of bentazon.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response (U.S. EPA, 1995a). Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to show the limitations of the risk assessment and to aid and guide the risk assessor in the ensuing steps of the assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 202-566-1676.

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This review document and summary information on IRIS have received peer review by EPA scientists and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an Agencywide review process whereby the IRIS Program Director has achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Planning, and Evaluation; and the Regional Offices.

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Summaries of the external peer reviewers' comments and the disposition of their recommendations are in Appendix A.

1. Introduction

This document presents the derivation of the noncancer dose-response assessments of bentazon for oral exposure (the oral reference dose or RfD), for inhalation exposure (the inhalation reference concentration or RfC), and the cancer hazard and dose-response assessments if appropriate data are available.

The RfD and RfC are meant to provide information on long-term toxic effects other than carcinogenicity. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other effects such as some carcinogenic responses. The RfD 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. The inhalation reference concentration (RfC) is analogous to the oral RfD. The inhalation RfC considers toxic effects within the respiratory system (portal of entry) and peripheral to the respiratory system (extrarespiratory or systemic effects). It is expressed in units of mg/m^3.

The carcinogenicity assessment is meant to provide information on three aspects of the carcinogenic risk assessment for the agent in question: the EPA classification and quantitative estimates of risk from oral exposure and inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. 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 estimate in terms of either risk per µg/L drinking water or risk per µg/m^3 air breathed. The third form is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for bentazon has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used include the following: the Risk Assessment Guidelines (U.S. EPA, 1987), the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991), (proposed) Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity (U.S. EPA, 1994a), (proposed) Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1995b), Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994b), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), The Use of the Benchmark Dose Approach in Health Risk Assessment (U.S. EPA, 1995a), Guidance on Risk Characterization (U.S. EPA, 1995c), and Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b).

Literature search strategies employed for this compound were based on the CASRN and 1at least one common name. As a minimum, the following databases were searched: FIFRA,1 1RTECS, GENETOX, TOXLINE, CANCERLINE, and MEDLINE backfiles. Any pertinent

scientific information submitted by the public as a consequence of the Federal Register notification on the development of the IRIS file for bentazon was also considered.

2. Chemical and Physical Information Relevant to Assessments

Chemical identity: 3-(1-methylethyl)-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide.
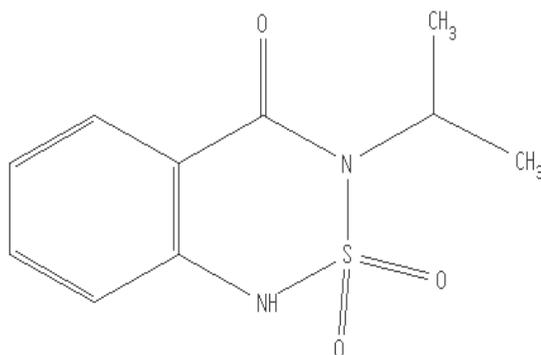
Figure 1. Structure of bentazon.

Common names: bentazon, bentazone, bendioxide.

Physical and chemical properties relevant to health and toxicological assessments (Worthing, 1983): Bentazon has a chemical formula of $C_{10} H_{12} N_2 O_3 S$, which provides a molecular weight of 240.3. Bentazon exists at room temperature as a colorless to slight brown crystalline powder with a melting point of from 137° to 139°C. Bentazon is not very volatile, having a vapor pressure at 20°C of $< 0.1 \times 10^{-7}$ mm Hg, and is only slightly soluble in water at 500 mg/L.

Bentazon is an herbicide used in agriculture for selective postemergence control of many broadleaf weeds in soybeans, rice, corn, peanuts, mint, dry beans, dry peas, and succulent lima beans.

3. Toxicokinetics Relevant to Assessments

3.1. Absorption

Bentazon has been tested for its ability to be absorbed both orally and dermally. A single gavage dose of bentazon of 4 mg/kg body weight was found to be rapidly absorbed in rats based on the finding of peak plasma levels from 0.5 to 2.0 h following the dosing. Less than 10% of the determined peak plasma values were present 10 h after the dosing (Chasseaud et al., 1972). Dermal absorption (amount penetrating and amount remaining in or on the skin) is variable, with only 1%-2% of the dermal dose penetrating the skin, as determined from the finding of the parent compound in the urine, with another 6%-61% determined to be retained on or in the skin. The

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excretion half-life was calculated to be 4 h, with most of the dose (> 90%) being found in the urine. No sex differences were noted for absorption or elimination times (Hawkins et al., 1986).

3.2. Distribution

Whole-body autoradiography of rats 1 h after oral dosing with 0.8 mg/kg body weight 14-C-bentazon indicated high levels of radioactivity present in the stomach, kidneys, liver, and heart (Chasseaud et al., 1972). Total radioactive residues in the body were less than 0.69% of the dose at 168 h after a single oral gavage dose of 3.8 or 205 mg/kg body weight.

3.3. Metabolism

Parent bentazon was the major form of bentazon found in the urine of orally dosed rats. It accounted for 77%-91% of the administered dose, while 8-hydroxybentazon accounted for 6.3% of the dose. Only minor (2% of dose) amounts of the isomer 6-hydroxybentazon were found in the urine (Hawkins et al., 1987).

In mice dosed orally with 14-C-bentazon, the cyclic sulfonamide ring of bentazon is apparently cleaved to several metabolites. These metabolites include N-isopropyl sulfamyl anthranilic acid (5.4%), anthranilic acid (6.2%), and 2-amino-N-isopropyl benzamide (6.1%). However, no 6- or 8-hydroxybentazon was detected in the urine of mice. The parent compound also accounted for about 71.3% of the administered radioactivity (Booth, 1974).

3.4. Excretion

Rats excreted 91% of a radioactive dose as parent compound in the urine and also eliminated 0.9% of the dose in the feces. At a dose of 3.8 or 205 mg/kg body weight, 0.8% or 2.3% of the radioactivity administered was eliminated in the feces over a 168 h period. Up to 95.9% of the radioactive dose was excreted in the urine, and the excretion half-life was calculated to be 4 h in rats (Hawkins et al., 1986). Similarly, urinary radioactivity accounted for approximately 93% of an orally administered dose in mice (Booth, 1974).

4. Hazard Identification

4.1. Studies in Humans

Bentazon use has not been tested for toxicity in humans via the oral route of exposure. However, because bentazon is used as a water-based spray, emergency medical cases and clinical reports might be expected in the future from accidental ingestion by children or agricultural workers. Incidence reports might also be expected in the future from inhalation exposure.

4.2. Subchronic and Chronic Studies and Cancer Bioassays in Animals

4.2.1. Subchronic Toxicity

Subchronic toxicity testing in several animal species has shown that bentazon produces a variety of substantive changes, including loss of blood into the intestinal tract and a derangement of the clotting mechanism.

A subchronic 90-day dog feeding study was reported (BASF AG, 1970a) with doses of 0, 100, 300, 1,000, and 3,000 ppm, which approximated 0, 2.5, 7.5, 25, and 75 mg/kg bwt/day, respectively. The study used limited numbers (3 per sex in each dose level) of test animals. The animals at the highest dose lost weight, became cachectic, developed diarrhea, and exhibited fresh blood in the feces by the end of the study. The dogs receiving 75 mg/kg bwt/day vomited frequently and appeared in generally poor health, to the extent that 1/3 of the males and 2/3 of the females died on study. Weight losses as well as blood chemistry values such as low serum albumin levels (as low as 2 g/100 mL compared with 3.6 g/100 mL at pretreatment) and elevated SGPT 49 mU/mL, BUN 15 mg/100 mL, SGOT 138 mU/mL, total bilirubin 0.43 mg/100 mL, and prolonged BSP excretion 30.3% compared with pretreatment values of 4.8%, SGPT 9.0 mU/mL, BUN 10.2 mg/100 mL, SGOT 56 mU/mL, and bilirubin 0.22 mg/1,l00 mL were reported for the highest dosed group. Though survival at termination was uneven in the distribution of sexes, some of the parameters (albumin, SGPT, BSP, and total protein) were starting to reflect the effects of the chemical by week 6, where the sample sizes were equal in both sexes.

Bentazon exposure resulted in significant ($p < 0.01$) reductions of mean group hemoglobin values to 8.6 g% compared to 14.4 g%, mean group red blood cells to 3.8 million/mm^3 compared to 5.4 million/mm^3, and mean group hematocrit values to 27.5% compared to 41.2% pretreatment values, respectively, at the 75 mg/kg bwt/day dose level by week 6 of the study. Additionally, an increase in mean group reticulocyte values (1.35%) occurred at 75 mg/kg/day when compared to the pretreatment control group value of 0.07%. These parameter changes were not reported at 1,000 ppm and lower dose levels in the study. Clotting times for the prothrombin tests were significantly lengthened, from 8.1 sec to 13.4 sec at 13 weeks. Clotting times were not affected at 6 weeks. Clinical tests indicated pathology of the liver occurred at 75 mg/kg bwt/day.

Microscopic inspection of organ tissues showed fatty infiltration of the heart and liver, necrotic congestion of the liver, and albuminous swelling of the kidneys at 75 mg/kg bwt/day. A finding of prostatitis was noted in all of the 75 mg/kg bwt/day dosed males and in 1 of 3 males in both the 25 mg/kg bwt/day and 7.5 mg/kg bwt/day groups. A NOAEL for this study was 2.5 mg/kg bwt /day, based on the prostatitis. The LOAEL is considered to be tentative for prostatitis at approximately 7.5 mg/kg bwt/day.

Tennekes et al. (1987) reported a study of bentazon technical grade given in the diet to Wistar rats (10/sex/dose) for 13 weeks at dose levels of 0, 400, 1,200, or 3,600 ppm (the average doses based on food intake were 0, 25.3, 77.8, and 243.3 mg/kg bwt/day for males and 0, 28.9, 86.1, and 258.3 mg/kg bwt/day for females, respectively). The treatment period lasted 13 weeks and was followed by a 4-week recovery period. The study showed minimally depressed body weights of approximately 5%-6% in 3,600 ppm-treated females over the 13-week period and was used to establish test doses for longer periods of time in other studies. Only the male rats given 243.3 mg/kg/day of bentazon at 13 weeks showed a prolonged prothrombin time of 30.2 sec, compared with 22.5 sec in the control group, and partial thromboplastin time of 15.8 sec

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compared to 13.5 sec in the control group. Males were more affected by clotting defects than were females. These changes returned to normal in a 4-week recovery period. Other hematologic parameters were unchanged in the study. Serum albumin was only slightly (though statistically) increased in male rats in the study at 13 weeks. Organ weights were increased in males only at the highest dose level (kidneys at 2.44 g compared to controls at 2.03 g [$p < 0.01$] and adrenals at 0.068 g compared to controls at 0.058 g [$p < 0.05$]). Females exhibited slight (n.s.) increases in liver weights at 6.56 g compared to 6.25 g in controls.

The NOAEL was 1,200 ppm (77.8 mg/kg bwt/day in males and 86.1 mg/kg bwt/day in females) and the LOAEL was 3,600 ppm (243.3 mg/kg bwt/day in males and 258 mg/kg bwt/day in females) based on the clotting time changes noted in the males and the loss of body weight by females at 3,600 ppm dose levels, respectively.

A subchronic study of 13 weeks duration with rats reported by BASF AG (1970b) did not indicate a bleeding problem in the intestinal tract of treated animals. However, the dose levels tested in this subchronic study were less than half those found in a preliminary 28-day study showing hemorrhage in the thymus at 2,000 ppm (approximately 100 mg/kg bwt/day based on an assumed 20 ppm equal to 1 mg/kg bwt/day conversion). This report was used only to establish dosing levels for longer term studies.

4.2.2. Chronic Toxicity and Cancer Bioassay

Several chronic studies have been reported that show effects of bentazon on the intestinal tract as well as hematological changes, body weight changes, and some organ weight changes through dietary exposure of the rat, mouse, and dog.

A chronic feeding toxicity study to evaluate the toxicity and potential carcinogenicity of bentazon in rats was performed by Takehara and Tajima (1984) using groups of Fischer 344/Du rats (70/sex/dose with a 6- and 12-month interim sacrifice of 10/sex/dose). They were fed bentazon (which by itself was stable up to 2 years under normal storage conditions) in the diet for 2 years at dose levels of 0, 200, 800, or 4,000 ppm (male: 0, 9, 35, or 180 mg/kg bwt/day; female: 0, 11, 45, or 244 mg/kg bwt/day).

Mean body weights of high-dose male and female rats were significantly ($p < 0.001$) lower than controls. In males receiving 35 mg/kg bwt/day, body weights were significantly ($p < 0.05$) lower than controls for most of the time between weeks 19 and 36. In females receiving 45 mg/kg bwt/day, mean body weights were significantly lower than controls only at weeks 60 and 65. Compound-related reductions in food consumption were also reported in mid- and high-dose males. Food consumption for high-dose males was significantly ($p < 0.05$) less than control values for 37 of the 104 weeks of the study. Mid-dose-level males also showed significant differences in food consumption for 20 of the 104 weeks. No compound-related changes in food consumption were observed for female rats at any dose levels.

Daily mean water consumption was significantly ($p < 0.001$) increased (by approximately 30%) over the control group values in high-dose male and female rats from week 26 throughout most of the study. For mid-dose animals, mean water intake was significantly increased most of

the time between weeks 33 and 77 in males and from week 29 onward in females, though not to the extent of the high-dose groups. Water consumption or urinary parameters were not significantly different in the low-dose groups compared to controls.

Changes in renal function appeared with exposure to bentazon. In animals sacrificed at 6 or 12 months, most of the differences in urinalysis results between dosed and control groups were related to increased water intake. These included significant increases in urine volume and significant decreases in specific gravity.

Organ weights and organ-to-body-weight ratios were determined in the treated animals and showed that absolute and relative mean thyroid weights were significantly ($p < 0.05$) decreased (22.3 mg compared to 26.6 mg in controls) at 6 months in the mid-dose group receiving 35 mg/kg bwt/day males, and in the high-dose group (20.8 mg compared to 26.6 mg in controls). The organ weight decreases in males were even greater at 12 months in both the mid- and high-dose groups. A dose-dependent decrease in both absolute and relative mean thyroid weights of females was suggested by the data at 12 months. However, only the mean absolute thyroid weight in the high-dose group of females was significantly ($p < 0.05$) lower when compared to controls. No significant differences in female thyroid weights were observed at 24 months. Absolute liver and spleen weights were also significantly ($p < 0.05$) decreased in high-dose males at 6, 12, and 24 months; relative weights were significantly decreased at 6 and 24 months.

Hematological changes included mean platelet counts, which were significantly ($p < 0.01$) though only slightly decreased (i.e., 610,000 mm^3 vs. 690,000 mm^3 in males and 590,000 mm^3 vs. 670,000 mm^3 in females) in high-dose males and high-dose females at 6 months. Only an increase in the high-dose males versus controls was reported at 24 months (1,000,000 mm^3 vs. 820,000 mm^3). Prothrombin times (PT) and partial thromboplastin times (PTT) were significantly ($p < 0.01$) longer than control values at 6 months (19.0 sec vs. 22.4 sec) and at 12 months in high-dose males (19.0 sec vs. 23.4 sec). Prolonged PTTs compared to controls were also observed at 12 months in both sexes at mid-dose and also in high-dose females. PTT values at 24 months in the males of the 4,000 ppm group remained elevated above control group values, though not by as much as at the 12-month period.

Neoplastic findings were reported for animals that either died or were sacrificed in extremis as well as those that were sacrificed at termination of the study. There were no increases in tumor incidence in dosed animals sacrificed at either 6 months or 12 months when compared to control animals. The report indicates that there was an apparent increased incidence of pheochromocytomas of the adrenal glands in females fed 4,000 ppm of bentazon in the diet and sacrificed at 24 months. However, the apparent response to the test material in the animals, with 0/31 (0%) in controls, 2/29 (7%) in the lowest dose group, 2/35 (6%) in the middle dose group, and 3/27 (11%) seen in the highest dose group was well within the historical range of this tumor in several different laboratories. The incidence of this tumor within the testing laboratory indicated that the reported apparent increase was well within the historical value of 26/203 (13%) for control female rats. The apparent effect of the chemical was discounted in this review because of a lack of dose-response increase except in the highest dose group and the incidence at the highest dose occurring within the historical control level reported. Females also exhibited an

increase in endometrial polyps; when compared with the concurrent controls at 8/31 (26%), low-dose group at 7/29 (24%), mid-dose group at 14/35 (40%), and high-dose group at 8/27 (30%), the mid-dose incidence appears increased. However, the historical data for the control animals at the testing laboratory were 45/203 (22%), which are lower than the concurrent controls (26%) in the study. The lack of a significant dose response suggests that the effect is a random happening and is not a tumorigenic response to the chemical. Chromophobe adenomas of the pituitary glands were significantly increased in the females sacrificed at 24 months, but only in the 200-ppm group (18/29 [62%] compared to 11/31 [35%] in controls). These incidences are not considered to be biologically significant because of the lack of a dose response at higher doses. Bentazon is considered to be negative for a carcinogenic response when given for 2 years in the diets of male and female rats.

Based on the hematological changes (PT and PTT) observed at mid-experiment at the mid-dose level, the NOAEL for systemic toxicity is 200 ppm (male: 9 mg/kg bwt/day; female: 11 mg/kg bwt/day) and the LOAEL is 800 ppm (male: 35 mg/kg bwt/day; female: 45 mg/kg bwt/day).

Bentazon was fed to 50/dose group male and female $B6C3F_1$ mice (Tajima et al., 1984) at levels of 0, 100, 400, or 2,000 ppm in the diet for 2 years (males: 0, 12, 47, or 242 mg/kg bwt/day; females: 0, 12, 48, or 248 mg/kg bwt/day). Though not in feed, bentazon was reported to be stable under normal room temperatures and storage conditions for up to 2 years. An additional 20/sex/group were included for interim sacrifices at 6 and 12 months. There were increased PT in males that received 47 mg/kg bwt/day or 242 mg/kg bwt/day (15.2 and 21.5 sec respectively vs. 13.5 sec in controls), and also increases in heart hemorrhage among the high-dose males (242 mg/kg bwt/day) that died during the study. There was a significant increase in calcification of the tunica albuginea of the testes (2 in controls vs. 12 and 35 in 47 mg/kg bwt/day and 242 mg/kg bwt/day groups, respectively) ($p < 0.01$) and an increase in islet cell hyperplasia of the pancreas in males receiving 42 mg/kg bwt/day (19) or 242 mg/kg bwt/day (22) of bentazon compared to 11 among controls. There was a transient, slight decrease in mean body weight, but there was no significant difference in longevity of any dosed group when compared to the controls. Body weights were variable and not consistently different in the high-dosed males (242 mg/kg bwt/day) when compared to controls. Organ weights of kidney (control 0.74 g, high dose 0.78 g) and thyroid (control 7.2 mg, mid-dose 8.6 mg) were increased significantly in males. There were no effects on body weights in dosed females. Increased liver weights were noted only in mid-dose females. Microscopic changes were not increased in the livers or kidneys of the mid-dose females.

Neoplastic findings originally reported in this study were subsequently requested by the State of California to be reread by a panel of pathologists. The liver and lung slides received an independent blind review by three pathologists (C, B, Y) and their findings were submitted to the Agency. The data from these reviewers are reported in Tables 1 to 3.

We conclude that the historical control data for liver tumors in $B6C3F_1$ mice provide evidence that there was no significant increase in the incidence of hepatocellular carcinomas or adenomas in the study, though there was a statistically significant finding for the trend test. However, the Fisher's exact test did not confirm that any group was significantly increased,

though the increase in adenomas at the 242 mg/kg bwt/day dose level approached the lowest ($p <$ 0.05) level of statistical significance. The incidence of adenomas at this dose was less than the three historical control values. This conclusion is based on the fact that the incidence of hepatocellular adenomas was much lower in the concurrent control male mice at only 9%, whereas the historical controls (3 studies) ranged from 26% to 66% of the animals tested; the top dose incidence was less than any of the controls in any of the three control studies.

Carcinoma incidence in the bentazon study did not increase with increasing dose levels. Additionally, the combined tumors were well within the range noted in the historical data. The doses were considered adequate to evaluate the carcinogenic potential of bentazon because of the systemic toxicity noted in the 47 mg/kg bwt/day and 242 mg/kg bwt/day dosed animals and because of the increased PT and increased incidence of hemorrhage of the liver and heart at the highest dose (242 mg/kg bwt/day). The NOAEL for systemic toxicity is 12 mg/kg bwt/day in male mice because of increased PT mid-study and an increase in islet cell hyperplasia of the pancreas and calcification of the testes over controls at 47 mg/kg bwt/day and above. The LOAEL is 400 ppm (47 mg/kg bwt/day) in male mice.

A 1-year feeding study was completed under Good Laboratory Practice (GLP) conditions (Allen et al., 1989) with bentazon in beagle dogs using 6/sex/dose at 0, 100, 400, and 1,600 ppm. These dose levels were equivalent to an average bentazon intake of 0, 3.2, 13.1, or 52.3 mg/kg bwt/day. The 1-year dog study has been used by the Office of Pesticide Programs to replace a 2-year study (up to half the lifetime of a beagle dog) because half a lifetime (approximately 6 to 7 years) would represent a chronic exposure in the beagle. It was found in retrospect examinations that very little, if any, further toxicity would be found in a longer term study than in a 1-year ("chronic") study, and any additional uncertainty factor (UF) values would not be necessary for RfD evaluations.

Table 1. Liver toxicity[a]

Tumors		0 ppm	100 ppm	400 ppm	2,000 ppm
Males					
Adenoma	C[b]	4	3	6	11
	B	4	3	6	12
	Y	4	4	8	10
Carcinoma	C	8	7	10	11
	B	10	7	10	10
	Y	9	7	10	11
Females					
Adenoma	C	2	0	0	1
	B	2	0	0	2
	Y	2	0	0	0
Carcinoma	C	3	1	6	1
	B	3	1	6	1
	Y	3	1	6	1

[a]Data are from only the terminal sacrifice; 50 tissues were examined in each group.
[b]Set of three pathologist evaluations.

Table 2. Hepatocellular tumor rates in male mice with statistical analysis[a]

Tumors	0 ppm	100 ppm	400 ppm	2,000 ppm
Adenomas	5/58 (9)	5/58 (9)	10/59 (17)	12/58 (21)
$p=$[b]	0.021[c]	0.629	0.142	0.057
Carcinomas	9/58 (16)	7/58 (12)	10/59 (17)	11/58 (19)
$p=$	0.214	0.394	0.516	0.403
Both	14/58 (24)	12/58 (21)	20/59 (34)	23/58 (40)
$p=$	0.014[c]	0.41	0.169	0.055

[a]Data are those of Yamate and include the terminal and 12-month interim sacrifice.
[b]statistical analysis involved Cochran-Armitage trend test and Fisher's exact test. Significance of trend denoted at control; significance of pairwise comparison denoted at dose level.
[c]$p < 0.05$ Note: first adenoma and carcinoma observed at 53 and 61 weeks respectively in the 0 ppm dose group.

Table 3. Historical control data for liver tumors with (%) incidence

	Study 1 (7/79-8/81)		Study 2 (12/86-6/88)		Study 3 (2/89-9/90)	
	M	**F**	**M**	**F**	**M**	**F**
N=	**60**	**60**	**60**	**60**	**60**	**60**
Hepatocellular adenoma (%)	33(55)	7(11.7)	33(66)	5(10)	13(26)	3(6)
Hepatocellular carcinoma (%)	15(25)	9(15)	2(4)	0	6(12)	1(1.6)
Combined	48/60	16/60	35/60	5/60	19/60	4/60
occurrence (%)	(80)	(26.6)	(58.3)	(8.3)	(31.6)	(6.6)

[a]Presented on only three studies reported by the NIBS testing facility.

There was a compound-related increase among males in the incidence of feces with red areas, reported by the study authors as bloody stools, but this was not confirmed as blood by chemical analysis because of timing of sample collections. The occurrence of the stools was 0/6 at 0 mg/day or 3.2 mg/kg bwt/day (controls), 1/6 at 13.1 mg/kg bwt/day, and 2/6 at 52.3 mg/kg/ bwt/day. The incidences of 1/6 in the mid-dose group and 2/6 in the high-dose group lack statistical significance, however, because of the small number of animals in each dose group. However, this apparent dose-related effect acquires biological significance in context of the toxic effects of bentazon on hemostasis noted in other studies with mice, rats, and dogs. Dietary administration of bentazon produced increased PT and/or PTT in dogs. Male beagles exhibited elevated PTT ($p < 0.05$) at 49.7 mg/kg bwt/day. Treatment-related clinical signs were restricted to the 49.7 mg/kg bwt/day group and were observed in 3 males and 1 female. These signs included emaciated appearance and dehydration, diarrhea, and marked anemia. Histopathological examination of the intestinal tract provided no indication of lesions that could have caused the

bleeding episodes. Other lesions found by microscopy were not considered out of the ordinary for control animals. There was a dose-associated presence of feces with red areas (considered by study authors to be blood) in dogs fed bentazon at 13.1 mg/kg/day and 52.3 mg/kg/day. There was an absence of red areas in feces at 0 and 3.2 mg/kg bwt/day. In view of the overt anticoagulant effect of bentazon at 35 to 50 mg/kg bwt/day in other species, it is difficult to discount the presence of red areas as not being treatment related. Therefore, the LOAEL can be established at 13.1 mg/kg bwt/day based on apparent toxic effects on hemostasis in male beagles. The NOAEL appears to be 3.2 mg/kg bwt/day.

4.3. Reproductive/developmental studies -- Oral

A two-generation reproduction study in Wistar/Han rats (Suter et al., 1989) fed diets containing bentazon at levels of 0, 200, 800, or 3,200 ppm (approximating 0, 15, 62, and 249 mg/kg bwt/day, respectively). The study produced data showing minor reductions in body weights in both generations among high-dose (249 mg/kg bwt/day) animals that were not statistically significant. Some tubular cell basophilia in the kidneys was noted in high-dose male and female rats. Parental toxicity in the study was observed at the highest dose level, 249 mg/kg bwt/day, with a NOAEL established at 62 mg/kg bwt/day. No adverse effects were seen on fertility, implantation sites, postimplantation loss, or offspring survival that could be ascribed to the chemical. However, pup weight gains and body weights were reduced throughout lactation at 62 mg/kg bwt/day and above, with a NOAEL established at 15 mg/kg bwt/day.

A study with Chinchilla rabbits dosed by gavage on days 6-16 of gestation with 0, 75, 150, or 375 mg/kg bwt/day showed no appreciable evidence of compound-related maternal toxicity. There were no changes in mean body weight, mean body weight gains, corrected body weight gain, food consumption, or overt clinical signs. However, one mid-dose doe showed a partial abortion, embryonic resorptions, and no living fetuses; this effect is considered probably treatment related because 2 of 2 pregnant does treated with 450 mg/kg bwt/day of bentazon in a range-finding study produced almost complete resorption of the observed embryos. There were no effects of bentazon administration on mean resorptions/doe, mean numbers of live fetuses/doe, mean fetal weights, or mean sex ratios in this study. Developmental toxicity was not observed at any dose level (LOAEL $>$ 375 mg/kg bwt/day) for gross, visceral, or skeletal findings. The maternal toxicity LOAEL is set at 375 mg/kg bwt/day based on the single doe showing resorption of embryos and is supported by the range-finding effects at 450 mg/kg bwt/day; the maternal NOAEL is 150 mg/kg bwt/day (Becker et al., 1986b).

Wistar rats were dosed by gavage on days 6-15 of pregnancy with 0, 40, 100, or 250 mg/kg bwt/day of bentazon technical grade (Becker et al., 1986a). At the highest dose, 250 mg/kg bwt/day, developmental toxicity was seen as a decrease in body weights of pups surviving to maternal sacrifice. Toxicity was also noted as an increase in postimplantation loss and fetal resorptions (controls 0.0/dam, high dose 1.8/dam, $p < 0.05$) and as a decrease in ossification of the phalangeal nuclei of the fore and hindlimb digits. The fifth sternebrae and cervical vertebra also exhibited a decreased ossification, with 5 or 3.8% in controls versus 19 or 15.8% at the high dose. The decrease in fetal body weight and delays in tissue maturation suggest that bentazon is a general fetal systemic toxicant. The maternal NOAEL was greater than the highest dose tested

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(250 mg/kg bwt/day). The developmental toxicity NOAEL was 100 mg/kg bwt/day, and the LOAEL was 250 mg/kg bwt/day.

4.4. Other Relevant Studies

4.4.1. *Mutagenicity*

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

1. Bentazon was negative in reverse mutation assays with Salmonella strains with and without (S9) at doses of 20-5,000 µg/plate and in E. coli WP2 uvrA with and without (S9) at levels of 10-1,000 µg/plate (Engelhardt, 1985a).

2. Bentazon was negative in the CHO/HGPRT forward mutation assays with and without rat liver (S9) mix at concentrations of 100-5,000 µg/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 bwt (Engelhardt, 1985b).

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

4.5. Evaluation of Noncancer Effects

The effects of ingestion of bentazon have been tested across several species using shorter term subchronic studies as well as longer term chronic studies. The chemical has generally produced a loss of body weight in the various test species, as well as toxicities that vary in severity, such as organ calcification, hyperplasia of various cellular components of organs, liver damage, and blood clotting derangements. Dogs appear to be the most systemically sensitive with toxicity to the vascular system (bleeding into the intestinal tract), loss of circulating red blood cell mass, and prolonged times for clotting mechanisms (LOAEL of 13.1 and NOAEL of 3.2 mg/kg bwt/day). Mice appeared to be least sensitive, with testicular calcification and pancreatic islet cell hyperplasia after dietary exposure (LOAEL of 47 mg/kg bwt/day and a systemic NOAEL of 12 mg/kg bwt/day), while the effect of bentazon on rats was intermediate, with a systemic effect on hematological parameters NOAEL of 9 mg/kg bwt/day and a systemic LOAEL of 35 mg/kg bwt/day in male rats. Continued exposure in these species caused episodes of bleeding. When testing for coagulation parameters such as PT and PTT was undertaken, a prolongation of coagulation times was seen compared with controls at doses from 13.1 mg/kg bwt/day in dogs to approximately 42 mg/kg bwt/day in mice. These values indicate that some hemostatic mechanism was compromised in the test animals and that not all species are affected at the same dose levels. Upon cessation of the test material exposure, clotting derangements and histopathological

changes in the liver returned to normal after a short recovery period. The exact cause of failure in hemostasis mechanisms has not been delineated.

4.6. Weight-of-Evidence Evaluation and Cancer Characterization

The potential human hazard for carcinogenicity of bentazon has been evaluated through two different animal species studies submitted to the Agency. The rat study showed no carcinogenic effect, as evidenced by the lack of any statistically significant increase in tumor types, and the mouse study showed a dose-related trend only in the incidence of a small number of hepatocellular adenomas and adenomas and carcinomas combined. In spite of this trend, the incidence at even the highest dose was small (borderline statistical significance) and was definitely smaller than in controls of the studies completed at the same time in the same laboratory. More rigorous evaluation of the data leads to the conclusion that bentazon is not carcinogenic in these species.

The evidence suggesting bentazon is not likely to produce a carcinogenic response in humans consists of genotoxic tests (including gene mutation, chromosomal aberration, and other genotoxicity studies), all of which were either negative or not reproducible. No highly reactive chemical species are known to be generated during the metabolism of bentazon. No structure-activity basis exists for the carcinogenicity of bentazon. A slight, but not statistically significant, increase in hepatocellular adenomas was noted in the mouse carcinogenicity study. Upon rereading of the tissue slides, three pathologists reported that numbers of tumors found were no more than those reported for the control groups. As a consequence of these facts, EPA indicated that no further genotoxicity or carcinogenicity testing is currently necessary (U.S. EPA, 1992). Bentazon is a Group E chemical under the current (1986) Guidelines for Carcinogen Risk Assessment. Under the proposed (1996) cancer guidelines, this chemical is characterized as *not likely to cause cancer to humans*.

4.7. Susceptible Populations

4.7.1. Possible Childhood Susceptibility

The question arises whether very young test animals may not be able to detoxify the chemical and thus may be more susceptible to the toxicity of bentazon. However, the studies do not support this thesis. Data in the various studies, with NOAELs of 100 mg/kg bwt/day and a LOAEL of 250 mg/kg bwt/day in adults, do not indicate that very young children should exhibit a significantly greater sensitivity to bentazon toxicity than adults.

4.7.2. Possible Gender Differences

Data in the rat chronic study and the beagle dog study suggest that the females of the species tested were slightly less affected by the chemical exposure than were the males. This is particularly true with the effect that was considered to be most significant with regard to toxicity and hazard to the animals (blood clotting mechanism and hemorrhaging into the intestines).

5. Oral Dose-Response Assessment

5.1. Oral Reference Dose (RfD)

The dietary exposure of test animals to bentazon is associated with several effects in the species tested. The effects reported in a subchronic 13-week feeding study in dogs (BASF AG, 1970a) in which a small number of animals were tested for each dose group, appear to progress with the length of exposure. Eventual weight loss, diarrhea, vomiting and mucous membrane irritation and, finally, severely compromised health occur. The effects are further confirmed by blood chemistry tests and hematological evaluations. Liver pathology, as evidenced by changes in blood chemistry parameters, and heart and kidney effects were noted on necropsy. The NOAEL for this study was 2.5 mg/kg bwt/day based on a LOAEL of 7.5 mg/kg bwt/day for prostatitis, which was considered to be a response to the chemical.

Wistar rats given bentazon in the diet for 13 weeks at 0, 400, 1,200, or 3,600 ppm (approximated 0, 26.6, 77.8, and 243.3 mg/kg bwt/day bentazon for males) showed reduced body weights in females and prolonged clotting times in males at the highest dose (Tennekes et al., 1987). Males appeared to be more sensitive to the alterations in blood clotting parameters than were females. The NOAEL was 77.8 mg/kg bwt/day and the LOAEL was 243.3 mg/kg bwt/day based on the depression of clotting times in the males.

A longer term 2-year study in rats fed diets containing levels of 0, 200, 800, or 4,000 ppm bentazon (Takehara and Tajima, 1984) indicated that the same types of hematological effects (clotting defects) occurred as in the subchronic tests, but the effects were more severe and occurred at lower doses. There appeared to be an increase in the incidence of pheochromocytomas and liver tumors in the study, which were evaluated and considered to not be the result of treatment. The NOAEL for the chronic rat study was 200 ppm, (9 mg/kg bwt/day) and the LOAEL was 800 ppm (35 mg/kg bwt/day).

The dog study (Allen et al., 1989) of 1 year exposed the animals to diets with 0, 100, 400, or 1,600 ppm of bentazon. The animals exhibited essentially the same adverse effects on the clotting system that were noted in the subchronic studies and the chronic rat study. Bleeding episodes were evident, especially in the male dogs, where reportedly bloody stools and red-colored feces were recorded. These signs were significant, as supported by the loss of blood, the reduced circulating red cell mass, and the increased clotting times. The NOAEL was determined to be 100 ppm (3.2 mg/kg bwt/day) and the LOAEL was established as 400 ppm (13.1 mg/kg bwt/day).

The RfD (oral) is supported by the subchronic and longer term (chronic) studies of the rat, which also report coagulation and hemorrhage events, and is established using the NOAEL of 3.2 mg/kg bwt/day for blood clotting changes and evidences of blood in the intestinal tract of the male dog. The RfD is established as 0.03 mg/kg bwt/day (see discussion 5.1.3 below).

5.1.1. Choice of Principal Study and Critical Effect
From the studies provided, one can determine that the longer studies with lower dosages provide appropriate data with which to establish a dose-response relation. An RfD can be

established using the species and sex tested with the lowest NOAEL—the male dog at 3.2 mg/kg bwt/day. The effect considered most critical was derangement of the hemostasis mechanism and hemorrhaging into the intestinal tract. Several other effects were also considered in establishing the appropriate endpoint for an RfD, including 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 (using 3/sex) occurred at 7.5 mg/kg bwt/day with a NOAEL of 2.5 mg/kg bwt/day, but is not considered to be a significant effect because the same effects were not reproduced in a larger (6/sex) and longer (1 year) study. The longer study did not negate the LOAEL of 7.5 mg/kg bwt/day of the subchronic study, 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 and intestinal blood loss problems in the male dog was considered most critical and occurred at the lowest dose level in the data set.

5.1.2. Method of Analysis

Only the mg/kg bwt/day NOAEL method with an appropriate UF was used in this evaluation because of the lack of data (small number of animals used) for the toxic effect in the appropriate (dog) species. The data were considered insufficient to evaluate the RfD by the benchmark method.

5.1.3. RfD Derivation

Subchronic studies in rats and mice as well as in dogs have generally reported tendencies of the animals to suffer a loss of normal blood clotting mechanisms when treated with high doses of bentazon for relatively short periods of time. An early study by BASF AG, Wyandotte Chemical Corp. (1970b) reported that a preliminary 28-day exposure of approximately 100 mg/kg bwt/day caused hemorrhage in the thymus of treated rats. More recently (Tennekes et al., 1987), in a 13-week study in rats, bentazon at doses of 243 mg/kg bwt/day caused blood clotting defects and depressed body weights. The NOAEL was 86.1 mg/kg bwt/day. A 90-day study with bentazon (BASF AG, 1970a) in the diets of dogs caused them to suffer significant weight losses and hematological changes indicating loss of circulating red blood cell mass. Clotting parameters were significantly affected at approximately 75 mg/kg bwt/day. Prostatitis was produced in the males at doses as low as 7.5 mg/kg bwt/day; the NOAEL was 2.5 mg/kg bwt/day.

Longer term studies have shown the same effects occurring, but generally at some lower dose level than in the subchronic studies. The exception is the prostatitis seen in the 90-day dog study with a NOAEL of 2.5 mg/kg bwt/day, which was not reproduced in the more recent and longer term study. This lack of reproducibility provides some doubt whether the prostatitis was a chemically induced effect or possibly resolved spontaneously in the longer study. Therefore the longer term study is used to establish the RfD.

The derivation of an RfD includes the application of various UF and modifying factors (MF). The RfD for bentazon utilizes a full 100-fold UF. This was discussed by Lehman and Fitzhugh (1954) and subsequently adopted by the National Academy of Sciences in the early 1960s. The 100-fold UF is used by the EPA's Office of Pesticide Programs. It is derived from the 10-fold UF normally used to account for intraspecies variability. An additional 10-fold UF is

used to account for the interspecies extrapolation to the human population. Additional MFs were not considered necessary to provide adequate safety for use of this chemical. The UF is generally limited to 100-fold when there is a full database of adequately completed studies.

Reproductive and developmental toxicity studies did not provide evidence that neonates or developing embryos are at any significantly increased risk when the NOAELs in those studies are compared to the NOAEL on which the RfD is based. Data in the rat two-generation study suggest that newborns may be only slightly more sensitive than parents in that study. However, the NOAELs of the rat species studies are so much higher than the NOAEL values of the dog study on which the RfD is established that an additional MF is not considered necessary to protect the unborn or newborn.

The NOAEL of 3.2 mg/kg bwt/day derived from the 1-year dog feeding study uses a 10-fold UF for consideration of intraspecies variation and a 10-fold UF for the consideration of interspecies variability. This provides the total UF of $10 \times 10 = 100$. The RfD is then calculated to be 0.032 mg/kg bwt/day. The last digit of the 0.032 is rounded off because of the medium confidence level that we believe the data provide; therefore, the RfD would be 0.03 mg/kg bwt/day.

5.2. Inhalation Reference Concentration (RfC)

There are no data with which to assess an RfC for bentazon.

5.3. Cancer Assessment

The Agency has evaluated animal studies involving both rats and mice for chronic periods of exposure. Though the data in the studies exhibited apparent increases in several tumor types, it was subsequently found that the tumor incidences were at rates that were normally found in the testing laboratory as historical control values.

Available studies on human exposures have not shown any evidence of a carcinogenic response. Additionally, mutagenicity testing data have not indicated a mutagenic potential of any concern for bentazon. The weight of the evidence indicates that the likelihood that bentazon is a significant hazard for carcinogenicity in humans is extremely low. The Agency's Cancer Peer Review Committee in the Office of Pesticide Programs has evaluated the database of bentazon and has concluded that under the current classification scheme (U.S. EPA, 1986), bentazon should be considered a class E chemical. Under the proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996) EPA would characterize bentazon as "a chemical not likely to be carcinogenic to humans."

Studies with which to evaluate the carcinogenic potential of bentazon through the inhalation or dermal route of exposure have not been required in the past because of the type and condition of the material used in agriculture.

6. Hazard Identification and Dose Response

6.1. Hazard Identification

The principal study in this RfD assessment (1-year dog feeding study) (Allen, et al., 1989) is medium to high in confidence and reported several toxic effects which were considered most relevant in the evaluation of Bentazon. These effects included intestinal bleeding and reduced clotting times which were observed in the males and were considered as indicative of a derangement of hemostatic mechanisms in the body. Although the cause of the bleeding disorder was not delineated, and the animal group sizes were relatively small, (6 per sex per dose); and the analysis for occult blood in the stool of the treated male dogs was not completed, these effects were considered relevant to humans. To date there have been no cases of human toxicity to Bentazon.

The data base for Bentazon is relatively complete and includes studies for subchronic, chronic, genotoxicity, kinetics, and metabolism as well as developmental and multigeneration reproduction toxicity. Most of the studies were well conducted by scientific standards of the time period and several studies provide many of the same types of endpoints.

Chronic studies do not indicate that there is a carcinogenic hazard from the use of bentazon. Additionally, developmental and reproductive toxicity studies do not indicate that the young or neonate are at greater risk than are older test animals or that there is a reproductive or developmental toxicity hazard from bentazon.

An RfC for inhalation exposure was not established for this assessment. There was no studies that could be used to set this value. Default exposure values generated by the Occupational, Residential Exposure Branch, Office of Pesticides Program are used to evaluate whether further testing on an individual use basis should be provided to the Agency.

6.2 Dose Response Assessment

From a subchronic 90-day feeding study in rats with an NOEL of 77.4 mg/kg bwt/day for clotting defects, and a second study of 28 days indicating hemorrhage in the tyhmus of rats at approximately 100 mg/kg bwt/day, the problem of bleeding and or clotting problems is noted in preliminary studies in the rat species.

Similarly, subchronic study in the dog indicated the lose of blood in the feces of test animals at the highest dose of 75 mg/kg bwt/day with a NOEL of 25 mg/kg bwt/day for this effect. Finally, chronic studies in mice for up to 2 years indicated that doses of 242 mg/kg bwt/day caused hemorrhage in the liver and heart of the males on the study. Additional clotting derangement occurred at 47 mg/kg bwt/day with a NOEL of 12 mg/kg bwt/day. A chronic, 2 year study in rats also indicated the effects of bentazon on the clotting time in animals 244 and 45 mg/kg bwt/day and supported a NOEL of 9 mg/kg bwt/day in male rats.

The last species to be examined here is the dog and is also noted to exhibit bleeding and clotting abnormalities which show the lowest NOEL at 3.2 mg/kg bwt/day. The dog study showed the lowest dose upon which to base the RfD.

6.3. Cancer Assessment

6.3.1. Hazard Identification

Bentazon was initially considered to present a carcinogenic potential by the fact that there were increases in the incidence of pheochromocytomas in the adrenal glands of rats in the chronic carcinogenicity study (Takehara and Tajima, 1984). There was also an apparent increase in the incidence of hepatocellular adenomas in mice (Tajima et al., 1984). These apparent increases were subsequently shown not to be significant when the data were evaluated by the Office of Pesticide Programs' Cancer Peer Review Committee (CPRC) (U.S. EPA, 1992).

6.3.2. Dose-Response Assessment

No dose-response assessment was performed on this compound. However, rat and mouse studies that showed apparent tumor increases were subsequently shown to have no significant carcinogenic effects. The data are sufficient and adequate to indicate that bentazon does not display a significant carcinogenic potential for humans.

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8. Appendices

Appendix A: Summary of and Responses to External Peer Review Comments

The Toxicological Review and IRIS summaries for bentazon have undergone both internal peer review by scientists within EPA and a more formal external peer review by scientists chosen by EPA in accordance with the Standard Operating Procedures for Peer Review (U.S. EPA, 1994c). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. The external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. A summary of significant comments made by the external reviewers and EPA's response to these comments follows.

(*1*) *General Comments*

Question 1. The reviewers were asked if they were aware of any other data or studies that were relevant (i.e., useful for the hazard identification or dose-response assessment) to the assessment of the adverse health effects, both cancer and noncancer, of this chemical.

Reviewers' response: One reviewer indicated he was not aware of other data and the other two reviewers indicated that there were other data (on other species that would not be used in these types of evaluations), as well as references on cumulative tumors in control species of rodents that would further support the conclusions that bentazon was not found to be carcinogenic.

Question 2. The reviewers were asked if the most appropriate critical effects had been chosen for the RfD and if the tumors observed were biologically significant and relevant to human health.

Reviewers' response: The three reviewers indicated that the appropriate effects had been chosen for the determination of the RfD and that the tumors were not of biological significance and that they were not relevant to human health.

Question 3. The reviewers were asked if the noncancer RfD assessment had been based on the most appropriate study or studies.

Reviewers' response: The reviewers reported that the RfD was based on the appropriate studies.

Question 4. The reviewers were told that in the RfD, studies included under the heading "Supporting/Additional Studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, and any evidence corroborative of the critical effect or establishing the comprehensiveness of the database with respect to various endpoints (such as reproductive/developmental toxicity studies). Therefore should other studies be included under the "Supporting/Additional" category? Or should some studies be removed?

Reviewers' response: The reviewers noted that they were not aware of other relevant studies to be included and that studies should not be removed from the document.

Question 5. The reviewers were asked whether there were other data that should be considered in developing the UFs or the MFs for the noncancer assessment.

Reviewers' response: The reviewers either had no comment or stated that other data were not necessary in developing the UFs or MFs. Additionally, the reviewers offered that the data did not support the use of different UFs.

Question 6. The reviewers were asked if the confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the studies chosen, the relevancy of the effects (cancer and noncancer) to humans, and the comprehensiveness of the database. Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?

Reviewers' response: One reviewer indicated that the statements presented a clear rationale, and the underlying assumptions and limitations were apparent, and the confidence statements were sufficiently complete. A second reviewer cited a need to know if the studies were produced under GLP in order to raise his confidence level in the data. The third reviewer noted that information presented did not allow him to determine if the red color in the dog feces could have been produced by the chemical itself or by its metabolites. He also indicated that this additional information might not alter the assessment of the health risk, but would add to his level of confidence in understanding the action and effects of bentazon.

The Agency notes that the document was deficient in reporting that study in which authors reported the presence of bloody stools. It has been the experience of the Office of Pesticides that chemical and metabolite discoloration of feces is a general discoloration and not streaking, as was reported in the original study. Additionally, though the study was not a GLP-type study, its authors do have the knowledge and experience to recognize the streaking of blood in the feces of experimental animals. The document has been altered to reflect this finding.

(2) Chemical-Specific Questions for Bentazon

Question 1. The reviewers were asked: What is your opinion on the nature of the red staining areas in dog feces as being either an indicator of exposure (e.g., being composed of bentazon itself) or a biological response to bentazon?

Reviewers' response: One reviewer stated that it appeared that the staining areas in the feces were a biological response to bentazon. A second reviewer noted basic agreement with the conclusion that the red areas in the dog feces are treatment related and should be considered to be of biological significance, even with the small number of animals and the lack of chemical confirmation of the nature of the staining (because of the finding of blood in another dog study), toxic effects on blood coagulation observed in other species. The third reviewer noted that the hematological effects were seen in rats, mice, and dogs and tends to reinforce the judgment that these are characteristic of bentazon. However, this reviewer also questioned whether the color

areas are from the bentazon or metabolites. He stated correctly that chemical-physical constant data were unavailable to adequately evaluate this aspect.

Agency Response: Although chemical-physical constant information was unavailable, there was information in the study report itself stating that the red-stained areas were from blood. In conjunction with the other report indicating hemorrhage into the intestinal tract, the Agency is able to conclude that the red areas should be considered biological changes on which to base a toxicity endpoint.

Question 2. Is all the evidence given in support of a hemostatic mechanism for bentazon toxicity consistent and biologically plausible?

Reviewers' response: The reviewers considered the data adequate to make a hemostatic mechanism for bentazon plausible, but considered it not unequivocally proven to be a unique toxic effect of this chemical. One reviewer considered the chemistry and toxicokinetics studies of bentazon to be lacking enough information to be able to include "all" the data.

(3) Overall Recommendation

Reviewer 1: Acceptable with minor revisions.
Reviewer 2: Acceptable as is.
Reviewer 3: Acceptable with possible minor revisions concerning chemistry and toxicokinetic information.

(4) Additional Comments Provided by Reviewers

Comment: One reviewer commented that it would be advisable to include the chemical structure of bentazon in the document.

Response to Comment: The Agency agrees that it is a needed addition to the document. The change has been made to the IRIS file.

Comment: Two reviewers commented on the usefulness of adding whether a study was performed under the guidance of GLP.

Response to Comment: The Agency agrees with the usefulness of such an addition. However, unless the study makes note of such a designation, it is almost impossible to say that those studies performed overseas were not done at the same level of competence as those designated as GLP. Most of the pesticides whose studies have been completed after 1989 are reported as having been completed or not under the GLP standards. GLP applies to studies (toxicology) started after October 16, 1989 (U.S. EPA, 1989).