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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sulfosulfuron - Report of the Cancer Assessment Review Committee

FROM: Jess Rowland 10/12/98
Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

TO: Tompkins, PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

And

Ed Zager
Chief, Registration Action Branch 1
Health Effects Division (7509C)

The Cancer Assessment Review Committee met on August 26, 1998 to evaluate the carcinogenic potential of Sulfosulfuron. Attached please find the Revised Final Cancer Assessment Document, due to an error in the Quantification Section of the 9/30/98 Final Document.

cc: Karl Baetcke
Luke Brennecke
Lori Brunsman
Bill Burnam
Marion Copley
Virginia Dobozy
Pam Hurley
Esther Rinde
Jess Rowland
Linda Taylor

CANCER ASSESSMENT DOCUMENT

REVISED FINAL - SUPERCEDES 9/30/1998 FINAL

Revised due to an error in the Quantification Section of the 9/30/98 Final Document. Please discard that version.

EVALUATION OF THE CARCINOGENIC POTENTIAL OF *SULFOSULFURON*

REVISED FINAL REPORT

October 16, 1998

*C*ANCER *A*SSESSMENT *R*EVIEW *C*OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

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DATA PRESENTATION: Linnea Hansen, Toxicologist

DOCUMENT PREPARATION: Jess Rowland, Executive Secretary

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

William Burnam, Chairman

Karl Baetcke

Virginia Dobozy

Pam Hurley

Marion Copley

Esther Rinde

Linda Taylor

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report and statistical analysis of data, respectively)

Luke Brennecke, Pathology Consultant

Lori Brunsman, Statistical Analysis

OTHER ATTENDEES: Alberto Protzel

CONTENTS

EXECUTIVE SUMMARY

On August 26, 1998, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of sulfosulfuron.

Dr. Linnea Hansen of Toxicology Branch 1 introduced the chronic toxicity/carcinogenicity studies in Sprague Dawley rats and the carcinogenicity study in CD-1 mice describing the experimental design; reporting on survival and body weight effects, treatment-related non-neoplastic and neoplastic lesions, statistical analysis of the tumor data, the adequacy of the dose levels tested; and presenting the weight-of- evidence for the carcinogenicity of sulfosulfuron. Dr. Hansen also discussed the toxicology, metabolism and mutagenicity studies as well as structure activity relationships.

Sulfosulfuron (technical, 98.4%) was administered in the diet to Sprague-Dawley rats at 0, 50, 500 or 5000 ppm (equivalent to 0, 2.4, 24.4 or 244.2 mg/kg/day, respectively) to males for 22 months and at 0, 50, 500, 5000 or 20,000 ppm (0, 3.1, 30.4 or 314.1 1296.5 mg/kg/day, respectively) to females for 22 months. Another group of 50 male rats fed at 20,000 ppm (1178.3 mg/kg/day) was sacrificed on study day 259 due to excessive mortality from the effects of urolithiasis. In the study with CD-1 mice, the animals received sulfosulfuron (technical, 98.4%) in the diet at levels of 0, 30, 700, 3000 or 7000 ppm (equivalent to doses of 0, 4.0, 93.4 393.6 or 943.5 mg/kg/day and 0, 6.5, 153.0, 634.9 or 1388.2 mg/kg/day, in males and females, respectively) for 78 weeks.

The Committee concluded that 5000 ppm was adequate for assessing the carcinogenic potential of sulfosulfuron in male rats based on the abnormal crystals in the urine and slightly increased incidences of kidney and urinary bladder calculi and related lesions as well as the increased incidence of mineralization of the heart, lung, pancreas and skeletal muscle. The intended high level of 20,000 ppm was considered excessive due to high mortality secondary to urolithiasis-related pathology. In females, 5000 ppm was considered to be adequate based on increased incidences of abnormal urinary crystals, and slightly increased incidences of renal pelvic epithelial hyperplasia and gastric pyloric lesions. The incidence of grossly visible calculi was also increased. At 20,000 ppm (highest dose tested), toxicity to the urinary tract was pronounced. Slightly increased mortality, decreased body weight/weight gain, emaciated appearance, slightly increased BUN, systemic mineralization, fibrous osteodystrophy of the femur and sternum and parathyroid hyperplasia were also observed.

The Committee concluded that 7000 ppm was adequate for assessing the carcinogenic potential of sulfosulfuron in male mice based on urinary tract pathology secondary to treatment-related urolithiasis which included mucosal epithelial hyperplasia, chronic inflammation and ulceration. Although no treatment-related toxicity was seen in females at this dose (7000 ppm), it was considered to be adequate since it is the Limit-Dose for carcinogenicity testing in mice.

In rats, evidence of carcinogenicity was demonstrated by the occurrence of 1 urinary bladder transitional cell papilloma and 1 urinary bladder transitional cell carcinoma in females at 5,000 ppm (314.1 mg/kg/day). The animals that had transitional cell tumors also had calculus formation and related urinary bladder pathology.

No bladder tumors were seen in females at the next highest dose (20,000 ppm, or 1296.5 mg/kg/day). The tumors were not fatal and the carcinoma was not metastatic. No bladder tumors were seen in males at 5000 ppm (244.2 mg/kg/day), the highest dose tested in this sex.

In spite of the lack of dose-response and low incidence (only one adenoma and one carcinoma each were observed in 60 female rats), the Committee considered the bladder tumors to be treatment-related because tumors of the urinary bladder transitional cell are infrequently observed in historical controls. Although the incidence of transitional cell papilloma was within the historical control range (1/814; mean, 0.12%; range, 0-2%) of the study laboratory, carcinoma was not even reported in the historical control evaluation. Incidences for both transitional papilloma and carcinoma (mean, 0.08%, range, 0-1.4%) were within the historical control range compiled by the supplier (Charles River Laboratories). However, carcinoma and papilloma were not observed (in the same study).

The statistically significant increase in the incidence of adrenal pheochromocytoma in males at 50 and 500 ppm was not attributed to treatment because: 1) of the lack of dose-response; 2) the incidence was within the range of historical control values (mean, 15.15%; range, 4 - 30%) and 3) the incidence of 0% in the concurrent controls was also considered to be unusually low.

In mice, evidence of carcinogenicity was associated with a statistically significantly increasing trend for the incidence of benign mesenchymal tumors of the urinary bladder in males and the occurrence of a renal adenoma in one male and one female..

The Committee attributed the urinary bladder tumor to treatment because: 1) the incidence (11%) at 7000 ppm showed pair-wise significance ($p=0.026$) and a significant trend ($p=0.000$); 2); it was outside the historical control incidences of the testing laboratory (mean, 0.11%, range 0-2%) and the supplier (mean, 0.26%, range 0-2.53%); and 3) was also outside values reported in the open literature (mean 0.375%, range 0-2%) on the spontaneous incidence of these tumors.

Benign mesenchymal tumors of the urinary bladder are reportedly unique to Swiss Webster or CD-1 mice. The exact etiology of these tumors is not known, but it has been suggested that obstruction (such as might occur with calculus formation) in the urinary bladder may cause distension and changes in the cell population of the lamina propria and/or subserosal layers, which may lead eventually to tumor formation.

The Committee considered the significance of the renal adenoma in one male mouse uncertain because it was within the historical control range in data provided by the study laboratory. However, a relationship to treatment was not discounted because the tumor was also found in a female mouse. It is also unusual for more than 1 tumor to occur in one study, but in one historical control group there were 2/71 males with renal adenoma. Therefore, the Committee considered the renal tumors to be treatment-related because: 1) renal adenoma is rarely observed spontaneously; 2) it was seen in both sexes in this study; and 3) no renal adenomas were reported in either sex in historical control data compiled by the supplier, Charles River.

The Committee noted that the benign mesenchymal tumors of the urinary bladder in treated animals occurred in animals that also had urinary calculi and/or urinary tract pathology consistent with effects of urolithiasis. For example, at 7000 ppm in males, 3/5 animals had calculus and all had urinary tract lesions consistent with the presence of urinary calculus. However, lack of calculi histologically can not rule out the possible presence of calculi lost during processing. The male with renal adenoma also had urinary calculus formation and urinary tract lesions; however, there were no urinary tract lesions in the female with renal adenoma.

The Committee concluded that the urinary bladder tumors observed in female rats and male mice and the renal adenoma observed in female mice were treatment-related, because the urinary tract was the primary target organ of sulfosulfuron in all species tested in subchronic or chronic studies and because the incidence of the tumors observed generally exceeded available historical control values from the study laboratory and/or from data collected by Charles River Laboratories.

The incidence of benign mesenchymal tumors of the urinary bladder in male mice at 7000 ppm also exceeded the spontaneous tumor incidence reported in published studies and was statistically significantly increased over concurrent controls. The relationship of the single benign mesenchymal tumor in males at 3000 ppm was considered uncertain, although it was considered possibly treatment-related because a dose-response was observed and no tumors were observed in male controls or the two lowest dose groups. The relevance of these tumors to human risk assessment was discussed, since they are reportedly unique to Swiss-derived mice such as CD-1. It was concluded that although these tumors may not be relevant to human risk assessment, there is insufficient information available to conclude that sulfosulfuron could not cause other types of bladder tumors in humans.

Although the Committee considered dosing in the rat and mouse long-term dietary studies to be adequate, the high dose of 20,000 ppm in female rats was considered excessive by some Committee members because of mineralization in many organs, which may have compromised normal physiological functions. This systemic effect is secondary to renal pathology. However, the dose at which the bladder tumors were observed, 5000 ppm, was considered adequate based on the observations of abnormal urinary crystals and a small, treatment-related increase in some urinary tract lesions. The discontinued high dose of 20,000 ppm in male rats was considered excessive. The dose selection in the rat study was questioned by the Committee: for example, some members noted that a dose group in between 500 and 5000 ppm or between 5000 and

20,000 ppm might have provided more information about the relationship of tumors to urinary calculus formation. The shift in excretion in the rat metabolism study from primarily urinary at the low dose to primarily fecal at the high dose may have reflected, in part, incomplete absorption of sulfosulfuron and an intermediate dose level below 20,000 ppm in the chronic/carcinogenicity study may have helped in characterizing the dose-response.

The Committee discussed the relationship of the urinary tract tumors to the presence of urinary tract calculi and associated pathology. At this time, the Agency has not published a policy for evaluation of urinary bladder tumors in the rodent. The published literature indicates that a number of bladder carcinogens in rodents are associated with calculus formation. It has been proposed that in the rodent, urinary calculus formation results in continual irritation to the bladder mucosa, followed by necrosis, increased cell proliferation, hyperplasia and eventually tumor formation. Epidermal growth factor (EGF) and its receptors are hypothesized to play a role in formation of some tumors. Rodents do not excrete stones as readily as humans because of differences in posture and anatomy. Prolonged presence of stones in the bladder may therefore predispose rodents to bladder tumors.

Although the Committee felt that the data were strongly suggestive of a relationship between calculus formation and bladder tumor formation (based on gross and microscopic pathology in animals with tumors, urinalysis data, and lack of evidence of mutagenicity or positive SAR data in the most closely related sulfonylurea compounds), the majority of the Committee did not consider the available data to be adequate to rule out other possible carcinogenic mechanisms. For example, the test material might be mitogenic in the absence of calculus formation, or might be a carbonic anhydrase inhibitor (although the urinalysis data do not provide evidence for the latter). The Committee concluded that additional studies would be needed to demonstrate a direct causal relationship between urolithiasis and tumor formation (e.g., analysis of urinary crystals and calculi; reversibility or "start-stop" studies). Furthermore, a relationship between urinary calculus formation and renal adenoma has not been shown.

Sulfosulfuron did not show genotoxic potential in the *in vivo* or *in vitro* mutagenicity assays.

Sulfosulfuron is a sulfonylurea herbicide and is structurally related to several other sulfonylurea compounds. As a group, these compounds do not show evidence of carcinogenicity among those that have been classified. There are also several sulfonylurea compounds that contain a triazine ring moiety which were classified as Group C carcinogens; however, the Committee considered the carcinogenic activity of these compounds to be related to the triazine structure and not appropriate for structure-activity comparisons with sulfosulfuron. Some sulfonamide drugs which are carbonic anhydrase inhibitors have been shown to cause urinary calculus formation and bladder tumors in rodents.

In accordance with the Agency's *Proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996), the Committee classified sulfosulfuron as a **likely human carcinogen.** The weight-of-evidence for this classification is as follows:

(i). occurrence of rare transitional cell papilloma and carcinoma of the urinary bladder in female rats;

(ii) occurrence of rare mesenchymal tumors of the urinary bladder in male as well as renal adenomas in male and female mice;

(iii) can not discount the relevancy of the observed tumors to human exposure.

The Committee recommended that a linear low-dose approach (q_1*) for human risk characterization and extrapolation of risk should be based on the incidence of benign mesenchymal tumors in male mice. Although all three tumor types were considered to be biologically significant, the mesenchymal tumors were selected for extrapolation since this is the only tumor type that exhibited statistical (positive trend and pair-wise) significance. This extrapolation, rather than an MOE approach, is warranted due to lack of data on mode of action. The Registrant should consult the Agency if they wish to conduct additional studies to support a mode of action for the carcinogenicity of sulfosulfuron.

HED is continuing to use the multistage model which calculates the q_1* potency factor due to inconsistencies and lack of consensus regarding the methods of low dose linear extrapolation discussed in the Agency's 1996 *Proposed Guidelines for Carcinogenic Risk Assessment.*

I. INTRODUCTION

On August 26, 1998, the Health Effects Division's Cancer Assessment Review Committee (CARC) evaluated the carcinogenic potential of sulfosulfuron. The Committee evaluated a combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats and a carcinogenicity study in CD-1 mice. Dr. Linnea Hansen of Toxicology Branch 1 presented the experimental design and results of these studies, statistical analysis of the tumor data, weight-of-evidence considerations, as well as the toxicology, metabolism, mutagenicity and structure-activity relationship data.

II. BACKGROUND INFORMATION

Sulfosulfuron (MON 31500), a sulfonylurea herbicide, is a new chemical. Its chemical name is 1-(4,6-dimethoxypyrimidin-2-yl)-3-[(2-ethylsulfonylimidazo{1,2-a}pyridin-3-yl)sulfonyl]urea. The chemical structure is shown below in Figure 1. The molecular weight is 470.8 g. Solubility in water is relatively low, particularly as pH deviates from neutrality (1,627 ppm at pH 7; 18 ppm at pH 5; 482 ppm at pH 9). **The PC Code No. is 085603** and the CAS No. is 141776-32-1.

Proposed uses are for control of weeds (1) in spring or winter wheat and (2) on non-crop sites such as roadsides, parks, apartment complexes, industrial sites and other public (non-crop) areas. The proposed end-use products contain 73.7% technical active ingredient (a.i.) in a wettable granule formulation. Application rates are very low, ranging from 25 to 70 mg a.i./hectare. Applications for wheat are done once per year. Non-food applications may be done more than once but not exceeding 70 mg a.i./hectare per season. Tolerances are proposed for wheat (grain, straw, hay and forage), milk, meat, muscle, meat by-products, fat, kidney and liver.

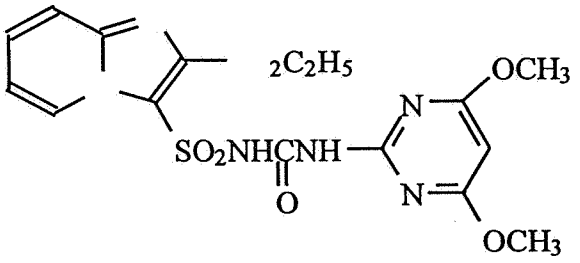

Figure 1: Sulfosulfuron

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study

Reference: Naylor, M.W. and Ruecker, F.A. (1997) Combined Chronic Toxicity/Oncogenicity Study of MON 37500 Administered in the Diet to Sprague-Dawley Rats. Monsanto Study No. ML-94-118. Laboratory Project No. EHL 94051. March 14, 1997. MRID 44295759. Unpublished study.

A. Experimental Design

Sulfosulfuron (98.4% a.i.) was continuously administered to 50 Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 50, 500 and 5000 ppm and to 50 females at 20,000 ppm for 22 months. Fifty males were also assigned at 20,000 ppm, but surviving animals were sacrificed on day 259 due to excessive mortality from the effects of urolithiasis. An additional 10 rats/sex/dose (except 20,000 ppm males) were assigned to an interim (12-month) sacrifice. Average daily intake of test material was 0, 2.4, 24.4 or 244.2 mg/kg/day for males up to 5000 ppm (1,178.3 for males at 20,000 ppm through day 259) and 3.1, 30.4, 314.1 or 1,296.5 mg/kg/day for females.

B. Discussion of Tumor Data

At 5,000 ppm, a urinary bladder transitional cell adenoma and carcinoma were each observed in one female (2 different animals, each 1 out of 60 animals; not statistically significant). These tumors were not observed in females at lower doses or at the highest dose tested (HDT) of 20,000 ppm, nor in males at any dose level.

In male rats, statistically significant increases ($p < 0.013$ and 0.014) in the incidence of adrenal pheochromocytoma were observed at 50 and 500, but not 5000 ppm. Table 1, below (extracted from Table 6 of quantitative risk analysis memorandum of Lori Brunsman) shows the rates for this tumor. Because a dose-response was not observed, these increases were not considered treatment-related. Historical control data from the supplier gave a mean incidence of 15.15% (range 4.0%-30.0%).

Table 1: Sprague-Dawley Male Rat Adrenal Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose			
	0 ppm	50 ppm	500 ppm	5000 ppm
Pheochromocytomas	0 mg/kg/day	2.4 mg/kg/day	24.4 mg/kg/day	244.2 mg/kg/day
Incidence	0/47	6/48	6/47	3[a]/49
%	0	12	13	6
p	0.420	**0.014***	**0.013***	0.129

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 52.

[a] First adrenal tumor observed at week 68, dose 5,000 ppm.

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

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Historical control data from the testing laboratory for the incidence of urinary bladder transitional cell tumors in Crl:CD BR® rats were provided. Data from 16 long-term studies conducted between 1982 and 1992 were available (all animals were from Charles River Portage, MI facility; in the sulfosulfuron study, all animals were from the Raleigh, NC facility). Transitional cell papilloma was observed in 0/808 males and in 1/814 females (mean incidence 0.12%; range 0%-2%). No transitional cell carcinomas were reported.

Historical control data on Crl:CD BR® rats have been published by the supplier, Charles River Laboratories. Animals were supplied by the Portage, MI, Kingston, NY, Lakeview, NJ or Montreal, Canada facilities and data were collected from independent testing laboratories. Among a total of 1,249 female rats from 19 groups in 24-month studies, 1 urinary bladder transitional cell papilloma and 1 carcinoma were observed (mean 0.08% incidence; range 0-1.4%). In male rats (19 groups, 1,250 animals), 1 papilloma (mean incidence 0.08%; range 0-1.4%) and 3 carcinomas (mean incidence 0.24%; range 0%-1.5%) were observed.

C Non-neoplastic Lesions

The incidences of selected non-neoplastic lesions in male and female rats are presented in Tables 2 and 3, respectively: The primary target organ of sulfosulfuron was the urinary tract in both males and females. In males at 5000 ppm, slight increases in the incidences of urinary calculi, dilated renal pelvis or urinary bladder and bladder mucosal epithelial hyperplasia were observed. Several other tissues (heart, pancreas, skeletal muscle, seminal vesicles) showed slight increases in mineralization. In the discontinued 20,000 ppm male group, urinary tissues of 21 animals were examined and a high incidence of urinary calculi and related lesions were observed. In females at 5000 ppm, the incidences of renal pelvic epithelial hyperplasia and gastric pyloric erosion/ulceration were slightly greater than controls. Statistically significant increases in several urinary tract lesions were observed at 20,000 ppm, including renal calculi, pelvic epithelial hyperplasia, pelvic dilatation and cortex/medulla mineralization and bladder mucosal epithelial hyperplasia. Ureters, with grossly visible stones, were examined and similar lesions were found. In addition to urinary tract effects at 20,000 ppm in females, mineralization in several tissues was observed. Parathyroid hyperplasia and fibrous osteodystrophy of the sternum and femur (12% vs. 0%, controls) were also seen at 20,000 ppm. At the interim sacrifice, there was no increase in the incidence of urinary tract lesions in males at 5000 ppm or below. In females at 20,000 ppm, calculi and/or mucosal epithelial hyperplasia were observed in a few animals. Grossly visible lesions were observed in a high percentage of males at 20,000 ppm (grossly visible calculi and dilated or enlarged renal pelvis or urinary bladder). Calculi were also observed in the ureter. Females at 5000 ppm had a slightly increased incidence of grossly visible urinary tract calculi and dilated renal pelvis, and these observations were more frequent at 20,000 ppm. Both females that developed transitional cell neoplasms also had urinary calculus formation (1 visible grossly; 1 grossly and microscopically) and related pathology.

TABLE 2: SELECTED NON-NEOPLASTIC LESIONS, IN MALE RATS FED SULFOSULFURON [a]

Organ/lesion	0 ppm 0 mg/kg/day	50 ppm 2.4 mg/kg/day	500 ppm 24.4 mg/kg/day	5,000 ppm 244.2 mg/kg/day	20,000 ppm 1178.3 mg/kg/day
Males					
Bladder, Mucosal epith. hyperpl.	6/56b	6/59	5/59	9 (15)	14/21 (67)
Dilatation	0/56 (0)	1/59	1/59	3 (5.0)	2/21 (10)
Calculus	0/56	0/56	0/59	0	2/21 (10)
Mineralization	1/56 (1.8)	0/56	0/59	0	4/21 (20)
Hemorrhage	0/56	0/56	0/59	2 (3.3)	3/21 (14)
Kidney, Pelvic calc./microcalc.	0/59	0/59	0/59	2 (3.3)	2/21 (10)
Dilatation, pelvis	8/59 (14)	7/59	7/59	3 (20)	21/21 (100)
Hyperplasia, pelvic epithelium	23/59 (40)	16/59	18/59	23 (38)	15/21 (71)
Mineralization, cortex/medulla	8/59 (14)	5/59	4/59	12 (6.7)	18/21 (86)
Mineralization, papilla	7/59 (12)	11/59	3/59	6 (10)	6/21 (29)
Necrosis, papilla	1/59 (1.7)	0/59	1/59	1 (1.7)	4/21 (19)
Hemorrhage, pelvis	0/59	0/59	1/59	0	3/21 (14)
Ureter, Dilatation	1/2 (50)	--	0/2	0/2	1/8 (13)
Hyperplasia	1/2 (50)	--	1/2	0/2	4/8 (50)
Heart,Mineralization,myocardium	5 (8.3)	3	3	9 (15)	--[c,d]
Mineralization, vascular	6 (10)	3	3	10 (17)	--
Lung, Random mineralization	1 (1.7)	0	0	4 (6.7)	--
Pancreas, Vascular mineralization	1/58 (1.7)	1/57	1/59	3/56 (5.4)	--
Skeletal muscle, Mineralization	3 (5.0)	1	4	9 (15)	--
Seminal vesicles, Dilatation	0/57	2/57	0	4 (6.7)	--
Inflammation	2/5 (3.5)	3/57	4	5 (8.3)	--

a Data extracted from Table 19, Appendix 2 and Table 12, Appendix 7, MRID 44295759. N = 60 unless otherwise indicated. Only some ureters with gross findings evaluated microscopically.

b Values in parentheses indicate percent incidence.

c -- No animals were evaluated.

d Data summarized by TB-I from individual animal data, Appendix 7, Table 12, MRID 44295759 (not analyzed statistically).

TABLE 3: SELECTED NON-NEOPLASTIC LESIONS IN FEMALE RATS FED SULFOSULFURON [a]

	0 ppm	50 ppm	500 ppm	5,000 ppm	20,000 ppm
Organ/Lesion	0 mg/kg/day	3.1 mg/kg/day	30.4 mg/kg/day	314.1 mg/kg/day	1296.5 mg/kg/day
Females					
Bladder, Mucosal epith. hyperpl.	2 (3.3)	2/59	0	3 (5.0)	10/57 (18)*
Kidney,Pelvic epith. hyperplasia	8 (13)	1/10	4	17 (28)	26 (43)**
Calculus/microcalc., pelvis	0	0/10	0	1 (1.7)	13 (22)**
Pelvic dilatation	1	1/10	2	8 (13)	20 (33)**
Pyelonephritis	1 (1.7)	1/10	2	1 (1.7)	7 (12)
Squam.metaplasia,pelvic epith.	0	0/10	0	0	5 (8.3)
Mineralization, cortex/medulla	3 (5.0)	0/10	4	3 (5.0)	17 (28)**
Suppurative inflammation	0	0	0	1 (1.7)	2 (3.4)
Ureter(s), Dilatation/distension	--	--	--	--	4/7 (57)
Inflammation	--	--	--	--	4/7 (57)
Hyperplasia, mucosal epith.	--	--	--	--	5/7 (71)
Calculi	--	--	--	--	2/7 (29)
Erosion/ulceration	--	--	--	--	1/7 (14)
Squamous metaplasia	--	--	--	--	2/7 (29)
Mineralization	--	--	--	-	1/7 (14)
Aorta, Mineralization	1 (1.7)	--	0	0	10 (17)*
Femur, Fibrous osteodystrophy	1 (1.7)	--	0	0	7 (12)
Sternum, Fibrous osteodystrophy	1 (1.7)	--	0	0	7 (12)
Eye, Corneal mineralization	0/59	--	0/58	1/59(1.7)	3/55 (6)
Heart, Myocardial mineralization	1 (1.7)	--	0	1 (1.7)	9 (15)*
Vascular mineralization	1 (1.7)	--	0	1 (1.7)	11 (18)**
Lungs, Random mineralization	1 (1.7)	0/10-	0	0	7 (12)

a Data extracted from Table 19, Appendix 2, MRID 44295759. N = 60 unless otherwise indicated.

b Values in parentheses indicate percent incidence.

c -- No animals were evaluated.

* Statistically significant, $p \leq 0.05$; ** $p \leq 0.01$. Lesions in ureter and mesentery not analyzed statistically.

D. Adequacy of Dosing for Assessment of Carcinogenic Potential

In males, 5000 ppm was considered to be adequate for assessing the carcinogenic potential of sulfosulfuron based on the abnormal crystals in the urine and slightly increased incidences of kidney and urinary bladder calculi and related lesions (dilatation of the renal pelvis and bladder, urinary bladder epithelial hyperplasia) as well as the increased incidence of mineralization of the heart, lung, pancreas and skeletal muscle. The intended high dose of 20,000 ppm, discontinued at day 259, was considered excessive due to high mortality secondary to urolithiasis-related pathology.

In females, dosing was considered adequate for assessing the carcinogenic potential of sulfosulfuron. At 5000 ppm (high-mid dose), increased incidences of abnormal urinary crystals, and slightly increased incidences of renal pelvic epithelial hyperplasia and gastric pyloric lesions were observed. The incidence of grossly visible calculi was also increased. At 20,000 ppm (highest dose tested), toxicity to the urinary tract was pronounced. Slightly increased mortality, decreased body weight/weight gain, emaciated appearance, slightly increased BUN, systemic mineralization, fibrous osteodystrophy of the femur and sternum and parathyroid hyperplasia were also observed. Some Committee members considered this dose excessive because mineralization in many organs, may have compromised normal physiological function.

2. Carcinogenicity Study in Mice

Reference: Naylor, M.W. and Thake, D.C. 1997. Oncogenicity Study of Sulfosulfuron Administered in Diet to CD-1 Mice for 18 Months. Monsanto Company (CEREGEN) Environmental Health Laboratory. Monsanto Study No. ML-94-119; Laboratory Project No. EHL 94052, MSL 15013. February 19, 1997. MRID 44295755. Unpublished study.

A. Experimental Design

Sulfosulfuron (98.4% a.i.) was administered continuously in the diet to 50 CD-1 albino mice/sex/dose at dose levels of 0, 30, 700, 3000 or 7000 ppm. An additional 10 animals/sex/dose were assigned to a 12-month interim sacrifice group. Average daily intake of test material was 0, 4.0, 93.4, 393.6 or 943.5 mg/kg/day for males and 0, 6.5, 153, 634.9 or 1,388.2 mg/kg/day for females.

B. Discussion of Tumor Data

There was a statistically significant increase in the incidences of benign mesenchymal urinary bladder tumors in male mice (see table 4). In males at 7000 ppm, the incidence of these tumors was statistically significantly increased ($p < 0.026$) in a pair-wise comparison with controls. A significant increasing trend ($p < 0.01$) was also observed. The incidence, from control to high dose, was 0%, 0%, 0%, 2% and 11%, respectively.

In females, tumors were identified in 1 control and 1 high dose animal. No statistically significant increases were observed in treated animals. Renal adenoma, a tumor that occurs infrequently in CD-1 mice, was found in 1 male and 1 female at 7000 ppm.

Table 4. CD-1 Mice: Male Urinary Bladder Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

Mesenchymal Bladder Tumors	Dose				
	0 ppm	30 ppm	700 ppm	3000 ppm	7000 ppm
	0 mg/kg/day	4 mg/kg/day	93.4 mg/kg/day	393.6 mg/kg/day	943.5 mg/kg/day
Incidence	0/45	0/46	0/48	1/47	5[a]/44
%	0	0	0	2	11
p	**0.000****	1.000	1.000	0.511	**0.026***

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.
[a]First mesenchymal tumor observed at week 70, dose 7000 ppm.
Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Historical control data from the testing laboratory for these tumors in CD-1 mice were available from 16 eighteen-month studies, including this study, initiated between 1984 and 1994). All animals (including the Sulfosulfuron study) were supplied by the Charles River Portage, MI facility. Benign mesenchymal tumors were found only in 1/910 males (mean incidence 0.11%; individual study incidence 0%-2%) and 0/911 females. Renal tubular adenoma was reported in a total of 4/956 males in 3 studies (mean incidence 0.42%; range 0%-3%) and in 0/953 females.

Historical control data on the CD-1 mouse have been published by the supplier, Charles River. Twelve groups of animals from 18-month studies conducted at independent contract toxicology laboratories were evaluated between December, 1984 and March, 1991. Animals were supplied by Charles River Facilities in the United Kingdom, Portage, MI, Kingston, NY or Wilmington, MA. Urinary bladder leiomyomas (another term used in this report, for benign mesenchymal urinary bladder tumors) were observed in 2/758 males (mean incidence 0.26%; range 0%-2.53%). In 726 females, these tumors were not reported. No benign or malignant neoplasms of the kidney were reported among 770 males or 770 females in 12 groups.

Published studies on urinary bladder benign mesenchymal tumors in Swiss or CD-1 mice were also submitted by the Registrant upon request. The report of Chandra and Frith, describes a low spontaneous incidence of these tumors in 400 male and 400 female control CD-1 mice from 8 studies: 3 female mice in 3 different studies (mean incidence 0.375%; range 0%-2%). These tumors have also been reported following urethral obstruction, implantation of paraffin pellets in the bladder or dietary administration of certain compounds.

C. Non-neoplastic Lesions

Selected non-neoplastic lesions in male mice are shown below in Table 5:

TABLE 5: SELECTED NON-NEOPLASTIC LESIONS IN MALE MICE FED SULFOSULFURON[1]

Organ/lesion	0 ppm	30 ppm	700 ppm	3,000 ppm	7,000 ppm
	0 mg/kg/day	4 mg/kg/day	93.4 mg/kg/day	393.6 mg/kg/day	943.5 mg/kg/day
Males					
Bladder, calculus/microcalculus	1/59	0/59	0/59	4/59	10*
Dilatation	5/59	4/59	3/59	8/59	20**
Hyperplasia, mucosal epithelium	4/59	1/59	2/59	25/59**	41**
					1**
Inflammation, chronic	2/59	3/59	2/59	23/59**	8*
Metaplasia, squamous	0/59	0/59	0/59	1/59	
Kidney, Atrophy	2	0/10	0/59	3/59	11*
Calculus/micro calculus, pelvis	1	0/10	0/59	1/59	3
Dilatation, pelvis	5	0/10	2/59	4/59	27**
Hyperplasia, pelvic epithelium	2	0/10	1/59	1/59	3
Hyperplas./regen., tubular epith.	46/59	8/10	48/59	38/59	46
Mineralization, tubular	38	7/10	39/59	34/59	33
Necrosis, papilla	0/59	0/10	0/59	2/59	2
Mononuclear infiltrate, interstitium/perivascular area	49/59	0/10	51/59	52/59	53
Ureter, calculus/microcalculus	--[2]	--	--	--	1/1
Heart, Fibrosis, myocardial	8	--	8	7	9
Inflammation, myocardial	3	--	4	1	2
Lung, Mononuclear infiltrate, peribronchiolar/perivascular	21	0/10	19	15	17

1 Data extracted from Table 18, Appendix 2, MRID 44295755). N = 60 unless otherwise indicated.

2 -- No animals were evaluated.

* significantly different from control (0.05); ** significantly different from control (0.01).

In male mice, the incidence of urinary tract calculus formation and related microscopic lesions of the bladder (including mucosal epithelial hyperplasia, chronic inflammation, ulceration and dilatation) was increased at 3000 and 7000 ppm at study termination. Kidneys also showed effects at 7000 ppm. No treatment-related non-neoplastic lesions were observed in female mice. Grossly visible calculi were observed in many males at 5000 ppm (21/60, bladder) and 7000 ppm (41/60, bladder and 21/60, kidney). Males with benign mesenchymal tumors of the urinary bladder had gross and microscopic lesions of the urinary tract consistent with urolithiasis. Calculi were observed in several animals with bladder tumors (at high dose, 3/5 males with tumors also had urinary calculi). The high-dose female with a benign mesenchymal tumor of the bladder also had calculus formation and related urinary tract pathology, the only female with these lesions. The male with a renal adenoma also had urinary calculus formation and related pathology; however, no kidney or bladder lesions were observed in the female with the renal adenoma. No treatment-related lesions were observed at the interim sacrifice in either males or females.

D. Adequacy of Dosing for Assessment of Carcinogenic Potential

The highest dose tested (7000 ppm) was considered adequate for assessing the carcinogenic potential of sulfosulfuron. In males, urinary tract pathology secondary to treatment-related urolithiasis were observed at 3000 and 7000 ppm and included mucosal epithelial hyperplasia, chronic inflammation and ulceration. Although, no treatment-related toxicity was seen in females at this dose (7000 ppm) since it is the Limit-Dose for carcinogenicity testing, dosing was considered to be adequate for assessing carcinogenicity.

IV. TOXICOLOGY

1. Metabolism

Sulfosulfuron was rapidly excreted (most of the administered dose was excreted within 72 hr post-dosing). Excretion at low doses was primarily via the urine (77%-87% of administered dose at 10 mg/kg), whereas at high dose, excretion was primarily via the feces (55%-63% at 1,000 mg/kg). Urinary elimination was biexponential (initial phase half life 2.2-5.8 hrs and terminal phase half-life 21.4-56.7 hrs); whole-body elimination showed similar kinetics. Absorption was essentially complete at the low dose (10 mg/kg) but limited at the high dose (1,000 mg/kg): it is unclear whether this was a dose-dependent effect or was due to incomplete solubility of the test material in the vehicle at the high dose. There was no significant accumulation of sulfosulfuron or its metabolites in tissues. Biotransformation was limited and most of the administered dose was excreted as unchanged parent compound. The primary routes of metabolism were demethylation and ring-hydroxylation to yield desmethyl and 5-hydroxy Sulfosulfuron metabolites. Low levels of imidazopyridine, pyrimidine and sulfonamide were detected in the urine and/or feces.

2. Mutagenicity

As shown below in Table 6, sulfosulfuron was shown to be non-mutagenic both *in vivo* and *in vitro* assays submitted to the Agency to satisfy Subdivision F Guidelines. An *in vitro* Chinese hamster lung point mutation assay (under review, 44280201), was positive, but only at precipitating and cytotoxic concentrations (≥1,000 μg/mL).

Table 6 Mutagenicity Studies with Sulfosulfuron

Assay Type	Concentration Tested / Metabolic Activation	Results	MRID No.
Gene Mutation Ames: *Salmonella* - strains TA98, TA100, TA102, TA1535 and TA1537	up to 5,000 μg/plate in the presence or absence of metabolic activation (rat liver S9).	Negative	44295760
In vitro Mammalian Cell Forward Gene Mutation (Chinese hamster ovary cells.	up to 5,000 μg/mL in the presence or absence of metabolic activation (rat liver S9)	Negative	44295761
In vitro Chromosomal Aberrations (Human lymphocytes).	Tested up to 1,000 μg/mL in the presence or absence of metabolic activation (rat liver S9).	Negative	44295762
In vivo Micronucleus (Mouse).	Tested up to 5,000 mg/kg.	Negative	44295763

4. Structure Activity Relationship

Sulfosulfuron is a sulfonylurea herbicide. Related sulfuron pesticides and their carcinogenicity classifications are shown below in Figure 2:

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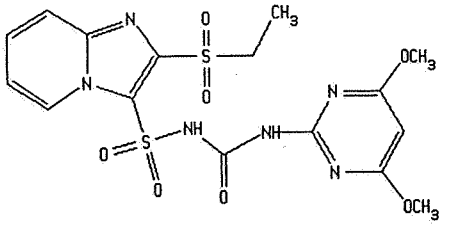
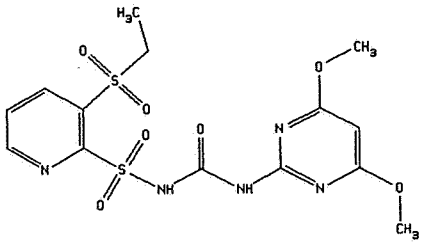
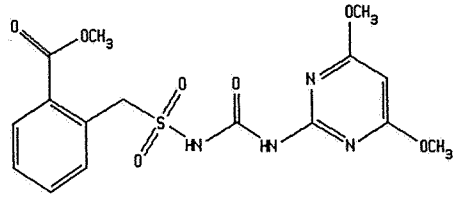
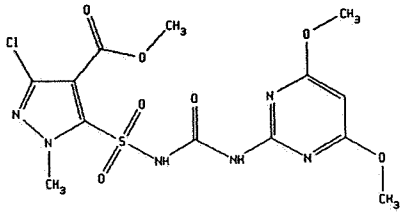
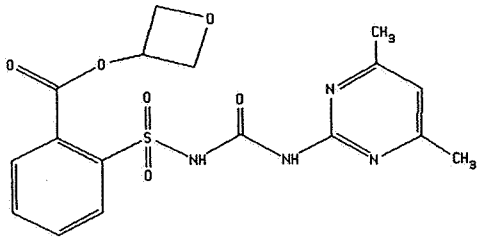
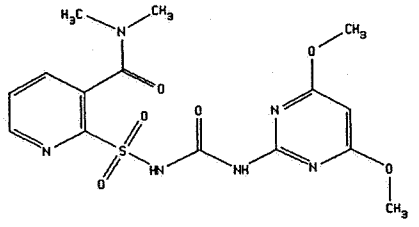
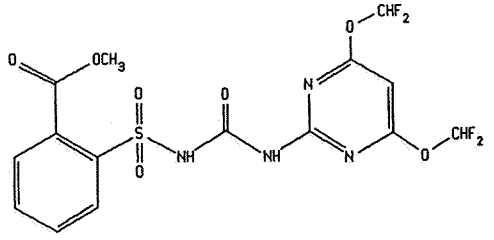
Figure 2. Pesticides Structurally Related to Sulfosulfuron

Name	Structure	Current OPP Classification
Sulfosulfuron PC No. 085601		Likely
Rimsulfuron PC No. 129009		E
Bensulfuron methyl PC No. 128820		Not Available
Halosulfuron methyl PC No. 128721		E

[a] From OPP's List of Chemicals Evaluated for Carcinogenic Potential dated 6/10/98

Name	Structure	Current OPP Classification[a]
CGA-277476 PC No. 122003		Not Available
Nicosulfuron PC No. 129008		E
Primisulfuron methyl PC No. 128973		D

[a] From OPP's List of Chemicals Evaluated for Carcinogenic Potential dated 6/10/98

The above sulfonylurea herbicides classified to-date do not show evidence of carcinogenicity. Of the 6 compounds related to Sulfosulfuron shown here, 3 were classified as E (not carcinogenic) and one as D (not classifiable, due to hepatocellular tumors in male mice at an excessive dose). Two others have not been classified.

There are also several other sulfonylurea herbicides with a triazine ring moiety. Two of these, were classified as C carcinogens (possible carcinogens): tribenuron-methyl (Express), based on mammary tumors in the female rat and trisulfuron-methyl, based on hepatocellular tumors in the male mouse. Others were assigned as D carcinogens (not classifiable) due to tumors at excessive dose levels (e.g., primisulfuron-methyl) or lack of dose-response in tumor incidence (e.g., prosulfuron). Because the triazine ring structure itself has been associated with carcinogenic activity, the sulfonylurea compounds containing this moiety were not considered appropriate for structure-activity relationship

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comparisons with Sulfosulfuron.

It was also noted that some sulfonamide drugs have been associated with urolithiasis and bladder tumors in rodents. Acetazolamide and ethylsulfonylnaphthalene-1-sulfonamide are both carbonic anhydrase inhibitors that cause urolithiasis and eventual tumor formation.

5. Acute, Subchronic and Chronic Toxicity

a Acute Toxicity Studies Technical and formulated Sulfosulfuron are classified as Toxicity Category IV for acute oral, inhalation and dermal toxicity and for primary dermal irritation. Sulfosulfuron is classified as Toxicity Category III for primary eye irritation and is not a dermal sensitizer (MRIDs 44295737 through 44295748).

Sulfosulfuron did not demonstrate neurotoxic potential and no other treatment-related effects were observed at dose levels up to 2,000 mg/kg in an acute neurobehavioral screening study in the rat (MRID 44295749).

b. Subchronic Toxicity Studies: Oral toxicity - In a 13 week toxicity study in the rat (MRID 44295750), Sulfosulfuron was administered continuously in the diet at dose levels of 0, 20, 200, 6,000 or 20,000 ppm (equivalent to average daily intake of 0, 1.2, 12.1, 123.2, 370.3 or 1,277.5 mg/kg/day, males and 0, 1.5, 4.6, 144.3, 447.5 or 1,489.2 mg/kg/day, females). Effects were observed only at 20,000 ppm. Decreased body weight/weight gain (-9.4%/-18%) were observed in males. Urolithiasis and related gross/microscopic lesions (including dilated renal pelvis, pyelonephritis, pelvic epithelial hyperplasia and urinary bladder mucosal epithelial hyperplasia) were observed in 2 females and 1 male. No treatment-related effects were observed in a subchronic neurotoxicity screening study in the rat (MRID 44295753); possible threshold decreases in body weight gain in males were observed at the highest dose tested, the threshold NOEL of 20,000 ppm (1,211 mg/kg/day).

In a 90-day oral toxicity study in Beagle dogs (MRID 44295751), sulfosulfuron was administered daily by gelatin capsule (5/sex/dose) at 0, 30, 100, 300 or 1,000 mg/kg/day. In females at 300 and 1,000 mg/kg/day and males at 1,000 mg/kg/day, abnormal urinary crystals were observed in several animals at day 45 and/or termination. One high dose male was sacrificed due to advanced urolithiasis with numerous related lesions in the urinary bladder, kidney and ureter. A second male had acute inflammation, erosions/ulcerations and edema of the urinary bladder. One female at 300 mg/kg/day and one at 1,000 mg/kg/day developed bladder lesions (hemorrhage, ulceration, inflammation and/or mucosal epithelial hyperplasia).

c. Chronic Toxicity Studies: In chronic toxicity study (MRID 44295754), beagle dogs (5/sex/dose) received gelatin capsules containing sulfosulfuron at 0, 5, 20, 100 or 500 mg/kg/day for 12 months. In males, abnormal urinary crystals were observed in 2 animals at 500 mg/kg/day. One of these males developed urinary calculi and urinary bladder lesions (hemorrhage, edema and thickened/irregular mucosa). No treatment-related effects were observed in females at any dose level.

The chronic toxicity studies in rats and mice are discussed in detail in Section III. Male and female Sprague-Dawley rats were fed diets containing sulfosulfuron (98.4% a.i.) at dose levels of 0, 50, 500, 5000 or 20,000 ppm (females only) for 22 months. Males at 20,000 ppm were sacrificed on study day 259 due to increased mortality (35% higher than controls). In females, mortality was slightly increased (16% higher than controls) at termination. Males at 20,000 ppm showed an increased incidence of blood color urine (37%) and intraabdominal swelling (25%). Decreased mean body weight/weight gain was also observed in both males (-9%/-12% by sacrifice) and females (up to -12%/-19%, days 51-485). At 5000 ppm, an increased incidence of abnormal urinary crystals (70-100% vs 10-40%, controls) in both sexes and possibly decreased serum albumin (-20%) in males were observed. In females at 20,000 ppm BUN was slightly increased at most time points (20% to 60% above controls) (MRID No. 44295759).

Male and female CD-1 mice received diets containing sulfosulfuron (98.4% a.i.) at dose levels of 0, 30, 700, 3000 or 7000 ppm. A statistical analysis of mortality indicated that there were no treatment-related effects on mortality in either sex. In males, clinical signs included urine-stained fur, intraabdominal swelling and abnormal penile erection (6-12 animals affected vs. 1-2, controls). In addition, grossly visible dilatation of the renal pelvis (45% vs. 8.3%, controls) and urinary bladder (45% vs. 8.3%, controls) were observed. No treatment-related effects were reported in females (MRID No. 44295755).

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

The Committee considered the following for a weight-of-evidence determination on the carcinogenic potential of sulfosulfuron:

1. Carcinogenicity

In rats, evidence of carcinogenicity was limited the occurrence of 1 urinary bladder transitional cell papilloma and 1 carcinoma in females at 5000 ppm (314.1 mg/kg/day). However, no bladder tumors were seen in females at the next highest dose (20,000 ppm or 1296.5 mg/kg/day). The tumors were not fatal and the carcinoma was not metastatic. No bladder tumors were seen in males at 5000 ppm (244.2 mg/kg/day), which was the

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highest dose tested in this sex without excessive toxicity.

At 5000 ppm, abnormal urinary crystals were observed in the urinalysis and a slightly increased incidence of microscopic lesions of the urinary tract and/or mineralization of non-urinary tissues were observed in both sexes. The animals that had transitional cell tumors also had calculus formation and related urinary bladder pathology.

In spite of the lack of dose-response and low incidence (only one adenoma and one carcinoma each were observed in 60 female rats), the Committee considered the bladder tumors to be treatment-related because tumors of the urinary bladder transitional cell are infrequently observed in historical controls. Although the incidence of transitional cell papilloma (1/814; mean, 0.12%; range, 0-2%) was within the historical control range of the study laboratory, the incidence of carcinoma was not. Incidences for both transitional papilloma and carcinoma (mean, 0.08%, range, 0-1.4%) were within the historical control range compiled by the supplier (Charles River). However, carcinoma and papilloma were not observed in the same study.

There was a statistically significant increase in the incidence of adrenal pheochromocytoma in males at 50 and 500 ppm (from control to high dose, 0%, 12%, 13% and 6%, respectively). The Committee did not attribute this increase to treatment because: 1) of the lack of dose-response; 2) the incidence was within the range of historical control values (mean, 15.15%; range, 4 - 30%) and 3) the incidence of 0% in the concurrent controls was also considered to be unusually low.

In mice, evidence of carcinogenicity was associated with a statistically significantly increasing trend for the incidence of benign mesenchymal tumors of the urinary bladder in males and the occurrence of a renal adenoma in one male and one female.

The Committee attributed the urinary bladder tumors to treatment because: 1) the incidence (11%) at 7000 ppm showed pair-wise significance ($p=0.026$) and a significant trend ($p=0.000$); 2) it was outside the historical control incidences of the testing laboratory (mean, 0.11%, range 0-2%) and the supplier (mean, 0.26%, range 0-2.53%); and 3) it was also outside values reported in the open literature (mean 0.375%, range 0-2%) on the spontaneous incidence of these tumors.

Benign mesenchymal tumors of the urinary bladder are reportedly unique to Swiss Webster or CD-1 mice. The exact etiology of these tumors is not known, but it has been suggested that obstruction (such as might occur with calculus formation) in the urinary bladder may cause distension and changes in the cell population of the lamina propria and/or subserosal layers, which may lead eventually to tumor formation.

The Committee considered the significance of the renal adenoma in one male mouse uncertain because it was within the historical control range in data provided by the study laboratory. However, a relationship to treatment was not discounted because the tumor

was also found in a female mouse. It is also unusual for more than 1 tumor to occur in one study, but in one historical control group there were 2/71 males with renal adenoma. Therefore, the Committee considered the renal tumors to be treatment-related because: 1) renal adenoma is rarely observed spontaneously; 2) it was seen in both sexes in this study; and 3) no renal adenomas were reported in either sex in historical control data compiled by the supplier, Charles River.

The Committee noted that the benign mesenchymal tumors of the urinary bladder in treated animals occurred in animals that also had urinary calculi and/or urinary tract pathology consistent with effects of urolithiasis. For example, at 7,000 ppm in males, 3/5 animals had calculus and all had urinary tract lesions consistent with the presence of urinary calculus. The male with renal adenoma also had urinary calculus formation and urinary tract lesions; however, there were no urinary tract lesions in the female with renal adenoma.

The Committee concluded that the urinary bladder tumors observed in female rats and male mice and the renal adenoma observed in female mice were treatment-related, because the urinary tract was the primary target organ of sulfosulfuron in all species tested in subchronic or chronic studies and because the incidence of the tumors observed generally exceeded available historical control values from the study laboratory and/or from data collected by Charles River Laboratories.

The incidence of benign mesenchymal tumors of the urinary bladder in male mice at 7000 ppm also exceeded the spontaneous tumor incidence reported in published studies and was statistically significantly increased over concurrent controls. The relationship of the single benign mesenchymal bladder tumor in males at 3,000 ppm was considered uncertain, although it was considered possibly treatment-related because a dose-response was observed and no tumors were observed in male controls or the two lowest dose groups. The relevance of these tumors to human risk assessment was discussed, since they are reportedly unique to Swiss-derived mice such as CD-1. It was concluded that although these tumors are not observed in humans, there is insufficient information available to conclude that sulfosulfuron could not cause other types of bladder tumors in humans.

Although the Committee considered dosing in the rat and mouse long-term dietary studies to be adequate, the high dose of 20,000 ppm in female rats was considered excessive by some Committee members because of mineralization in many organs, which may have compromised normal physiological functions. This systemic effect is secondary to renal pathology. However, the dose at which the bladder tumors were observed, 5,000 ppm, was considered adequate based on the observations of abnormal urinary crystals and a small, treatment-related increase in some urinary tract lesions. The discontinued high dose of 20,000 ppm in male rats was considered excessive.

The dose selection in the rat study was questioned by the Committee: for example, some members noted that a dose group in between 500 and 5,000 ppm or between 5,000 and 20,000 ppm might have provided more information about the relationship of tumors to urinary calculus formation. The shift in excretion in the rat metabolism study from primarily urinary at the low dose to primarily fecal at the high dose may have reflected, in part, incomplete absorption of sulfosulfuron and an intermediate dose level below 20,000 ppm in the chronic/carcinogenicity study may have helped in characterizing the dose-response.

The Committee discussed the relationship of the urinary tract tumors to the presence of urinary tract calculi and associated pathology. At this time, the Agency has not published a policy for evaluation of urinary bladder tumors in the rodent. The published literature indicates that a number of bladder carcinogens in rodents are associated with calculus formation. It has been proposed that in the rodent, urinary calculus formation results in continual irritation to the bladder mucosa, followed by necrosis, increased cell proliferation, hyperplasia and eventually tumor formation. Epidermal growth factor (EGF) and its receptors are hypothesized to play a role in formation of some tumors. Rodents do not excrete stones as readily as humans because of differences in posture and anatomy. Prolonged presence of stones in the bladder may therefore predispose rodents to bladder tumors.

Although the Committee felt that the data were strongly suggestive of a relationship between calculus formation and bladder tumor formation (based on gross and microscopic pathology in animals with tumors, urinalysis data, and lack of evidence of mutagenicity or positive SAR data in the most closely related sulfonylurea compounds), the majority of the Committee did not consider the available data to be adequate to rule out other possible carcinogenic mechanisms. For example, the test material might be mitogenic in the absence of calculus formation, or might be a carbonic anhydrase inhibitor (although the urinalysis data do not provide evidence for the latter). The Committee concluded that additional studies would be needed to demonstrate a direct casual relationship between urolithiasis and tumor formation (e.g., analysis of urinary crystals and calculi; reversibility or "start-stop" studies). Furthermore, a relationship between urinary calculus formation and renal adenoma has not been shown.

2. Mutagenicity

Sulfosulfuron did not show genotoxic potential in the *in vivo* or *in vitro* mutagenicity assays. (A Chinese hamster lung point mutation study which was not submitted was reported by the Registrant to be positive at, but not below, precipitating dose levels. The Committee requested that this study be submitted as confirmatory data.

3. Structure Activity Relationship

Sulfosulfuron is a sulfonylurea herbicide and is structurally related to several other sulfonylurea compounds. As a group, these compounds do not show evidence of carcinogenicity among those that have been classified. There are also several sulfonylurea compounds that contain a triazine ring moiety which were classified as Group C carcinogens; however, the Committee considered the carcinogenic activity of these compounds to be related to the triazine structure and not appropriate for structure-activity comparisons with sulfosulfuron. Some sulfonamide drugs which are carbonic anhydrase inhibitors have been shown to cause urinary calculus formation and bladder tumors in rodents.

VII. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the Agency's *Proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996), the Committee classified sulfosulfuron as a **likely human carcinogen.** The weight-of-evidence for this classification are as follows:

(i). occurrence of rare transitional cell papilloma and carcinoma of the urinary bladder in female rats;

(ii) occurrence of rare mesenchymal tumors of the urinary bladder in male as well as renal adenomas in male and female mice;

(iii) cannot discount the relevancy of the observed tumors to human exposure.

VIII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The Committee recommended that a linear low-dose approach (q_1*) for human risk characterization and extrapolation of risk should be based on the incidence of benign mesenchymal tumors in male mice. Although all three tumor types were considered to be biologically significant, the mesenchymal tumors were selected for extrapolation since this is the only tumor type that exhibited both a postivie trend and pair-wise significance. This extrapolation, rather than an MOE approach, is warranted due to lack of data on mode of action. The Registrant should consult the Agency if they wish to conduct additional studies to support a mechanism of carcinogenicity of sulfosulfuron.

HED is continuing to use the multistage model which calculates the q_1* potency factor due to inconsistencies and lack of consensus regarding the methods of low dose linear extrapolation discussed in the Agency's 1996 *Proposed Guidelines for Carcinogenic Risk Assessment.*

IX BIBLIOGRAPHY

MRID No.	CITATION
44295749	Branch, D.K., Thake, T.A., Kaempfe T.A. and Li, A.A. (1997) Acute Neurotoxicity Study of MON 37500 in Sprague-Dawley Rats. CEREGEN, Monsanto Company Environmental Health Laboratory (St. Louis, MO). Study No. ML-95-286; Laboratory project number EHL 95100; MSL 14959, January 30, 1997. (Unpublished Study.
44295750	M.W. Naylor and D.C. Thake (1995) Pilot Three Month Study of MON 37500 Administered in Feed to Sprague-Dawley Rats. Monsanto Company Environmental Health Laboratory (St. Louis, MO). Study No. ML-93-63; Laboratory Project No. EHL 93002. February 22, 1995. MRID 44295750. (Unpublished Study).
44295751	Naylor, M.W. and Thake, D.C. Summary: Naylor, M.W., (1996). Three Month Study of MON 37500 Administered by Capsule to Beagle Dogs. CEREGEN, A Unit of Monsanto Company Environmental Health Laboratory (EHL) St. Louis, Missouri 63110 (U. S. A.)EHL report# 94108, Monsanto# ML-94-324. MRID 44295751, 8 January 1996. (Unpublished Study)..
44295754	Naylor, M.W. and Ruecker, F.A. (1997) One Year Study of MON 37500 Administered by Capsule to Beagle Dogs. Monsanto Company Environmental Health Laboratory (St. Louis, MO). Monsanto Study No. ML-95-199, Laboratory Project No. EHL 95042 MSL 15007. February 5, 1997. MRID 44295754. (Unpublished Study).
44295755	Naylor, M.W. and Thake, D.C. 1997. Oncogenicity Study of Sulfosulfuron Administered in Diet to CD-1 Mice for 18 Months. Monsanto Company (CEREGEN) Environmental Health Laboratory. Monsanto Study No. ML-94-119; Laboratory Project No. EHL 94052, MSL 15013. February 19, 1997.. (Unpublished Study).
44295759.	Naylor, M.W. and Ruecker, F.A. (1997) Combined Chronic Toxicity/Oncogenicity Study of MON 37500 Administered in the Diet to Sprague-Dawley Rats. Monsanto Study No. ML-94-118. Laboratory Project No. EHL 94051. March 14, 1997. (Unpublished Study).
44295760	Stegeman, S.D., Warren, J. and Kier, L.D. (1995). Ames/Salmonella Mutagenicity Assay of MON 37500; Environmental Health Laboratory, Monsanto Co.; Study No. ML-94-004; Study Completion Date: March 15, 1995. (Unpublished Study).
44295761	Stegeman, S.D., Kier, L.D., Asbury, K.L., Garrett, S.L. and McAdams, J.G. (1996). CHO/HGPRT Gene Mutation Assay of MON 37500; Monsanto Co.

Environmental Health Laboratory, St. Louis, MO; Study No. ML-95-200; Study Completion Date: January 5, 1996. (Unpublished Study).

44295762 Murli, H. (1996) Chromosome Aberration Study in Human Whole Blood Lymphocytes with a Confirmatory Assay with Multiple Harvests with MON 37500. Corning Hazleton Inc. (CHV), Laboratory Project No. 17146-0-449CO, Final Report dated March 11, 1996. (Unpublished Study).

44295763 Stegeman, L. D.; Kier, L. D.; Garrett, S. L.; McAdams, J. G.; Warren, J. and Schermes, S. (1995) Mouse Bone Marrow Micronucleus Assay of MON 37500, performed at Monsanto's Environmental Health Laboratory (EHL), Lab Project No. EHL 94003/Monsanto Study No. ML-94-005, Final Report dated March 1, 1995 (Unpublished Study).

44295764 Stegeman, L. D.; Kier, L. D.; Albin, L. A. and Lau, H. (1996) Mouse Bone Marrow Assay of ^{14}C Radiolabeled MON 37500, performed at Monsanto's Environmental Health Laboratory (EHL), Lab Project No. EHL 95106/Monsanto Study No. ML-95-289, Final Report dated April 8, 1996 (Unpublished Study).

44295765 H. Lau, M.L. Kinnett, L.A. Albin, J. Warren, R.C. Chott, H. Fujiwara, R.G. Nadeau and M. E. Holland, The Absorption, Distribution, Elimination and Metabolism of MON 37500 in Sprague-Dawley Rats Following Oral and Intravenous Administration. (1996), Environmental Health Laboratory. Laboratory report number 93041, Monsanto Study# 14300, January 5, 1996. (Unpublished Study).

Chandra, M. And Frith, C.H. (1991). Toxicologic Pathology 19:164-167