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WASHINGTON, D.C. 20460

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

TXR No.: 0054463

MEMORANDUM

DATE: October 26, 2006

SUBJECT: ORTHOSULFAMURON: Report of the Cancer Assessment Review Committee

PC Code: 108209

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Karlyn Bailey, Toxicologist/Risk Assessor
Registration Action Branch 2, Health Effects Division (7509P)

Jim Tompkins, PM
Erik Kraft, Reviewer
Herbicide Branch, Registration Division (7505P)

The Cancer Assessment Review Committee met on September 20, 2006 to evaluate the carcinogenic potential of Orthosulfamuron. Attached please find the Final Cancer Assessment Document.

cc: J. Pletcher
Y. Woo

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
ORTHOSULFAMURON

PC CODE 108209

October 26, 2006
FINAL

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

DATA PRESENTATION _____
Karlyn Bailey, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell
Jessica Kidwell, Executive Secretary

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

Lori Brunsman, Statistician _____

William Burnam, Chair _____

Marion Copley _____

Vicki Dellarco _____

Kit Farwell _____

Abdallah Khasawinah _____

Nancy McCarroll _____

Jess Rowland _____

Linda Taylor _____

NON-COMMITTEE MEMBERS IN ATTENDANCE (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist See attached sheet

OTHER ATTENDEES: Kevin Crofton (EPA/NHEARL) (conference call)

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

On September 20, 2006 the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Orthosulfamuron.

Karlyn Bailey of Registration Action Branch 2 presented the chronic toxicity/carcinogenicity study in Han Wistar rats and the carcinogenicity study in CD-1 mice. In the chronic toxicity/carcinogenicity study, Orthosulfamuron (98.6-98.8% a.i.) was administered in the diet to 70 Han Wistar (HsdBrl Han:Wist) rats /sex/dose at nominal concentrations of 0, 1, 5, 500, or 1000 mg/kg/day for up to 2 years. Twenty rats/sex/dose were sacrificed at Week 52, and the remaining survivors were sacrificed at Week 104. In the mouse carcinogenicity study, Orthosulfamuron (98.0% a.i) was administered in the diet to 50 Crl:CD-1^{TM} (ICR)BR mice/sex/dose at nominal concentrations of 0, 100, 500, or 1000 mg/kg/day for up to 78 weeks. She also presented information on mutagenicity, structure activity relationship and mode of action data for the thyroid follicular cell tumors.

The CARC concluded the following:

Carcinogenicity

Rat

• In male Han Wistar rats, the incidences of thyroid follicular cell adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 1, 5, 500 and 1000 mg/kg/day dose groups were as follows:

Adenomas	1/50 (2%), 2/50 (4%), 1/50 (2%), 7/50 (14%), 10/49 (20%)
Carcinomas	0/50 (0), 1/50 (2%), 1/50 (2%), 0/50 (0), 0/49 (0)
Combined	1/50 (2%), 3/50 (6%), 2/50 (4%), 7/50 (14%), 10/49 (20%)

Male rats had significant positive trends ($p<0.01$) as well as significant differences in the pair-wise comparisons of the 500 mg/kg/day ($p<0.05$) and 1000 mg/kg/day ($p<0.01$) dose groups for adenomas and adenomas and carcinomas combined. The incidences of adenomas at the 500 and 1000 mg/kg/day dose groups exceeded the historical control ranges for the testing laboratory (0-12.5%) as well as for Charles River Laboratories (1.67-12.73%). Therefore, the CARC considered the thyroid follicular cell tumors (driven by adenomas) observed at 500 and 1000 mg/kg/day to be treatment-related.

• No treatment-related tumors were observed in female Han Wistar rats.

• The CARC concluded that dosing of male and female rats at the high dose of 1000 mg/kg/day was adequate, but not excessive, to assess the carcinogenicity of orthosulfamuron because the study was conducted at the limit dose. In addition, decreased body weight gains (32-38% during the second year; 12-20% over the entire

study) in both sexes and slight hepatotoxicity and nephrotoxicity were observed at 1000 mg/kg/day.

Mouse

- There were no treatment related tumors observed in either male or female CD-1 mice.

- The CARC concluded that dosing of male and female mice at the high dose of 1000 mg/kg/day, was adequate, but not excessive, to assess the carcinogenicity of orthosulfamuron because the study was conducted at the limit dose. Increased liver weights and increased incidence of centrilobular hepatocyte hypertrophy and centrilobular hepatocyte vacuolation were observed in males. Although the high dose of 1000 mg/kg/day in this mouse study did not result in systemic toxicity in females, the study was adequate because the limit dose was tested.

Mutagenicity

The overall results indicate that neither the parent compound nor metabolites IR7863 or IR7825 are mutagenic. In contrast, metabolite IR8181 was positive for the induction of structural chromosome aberrations at concentrations that were minimally cytotoxic. However, there is no concern for mutagenicity at this time because the evidence of *in vitro* mutagenicity is not expressed in the whole animal.

Structure-Activity Relationship

The very limited SAR data were not useful in the weight-of-evidence analysis.

Mode of Action

While it is plausible that exposure to orthosulfamuron may cause thyroid tumors via perturbation of thyroid-pituitary functioning due to enhanced hepatic clearance of thyroxin, the thyroid hormone data, which are critical to delineating a sequence of key events leading to tumor formation, are inadequate. The reduction in both circulating serum T4 and T3 and subsequent increase in TSH, as typically seen with a disruption in thyroid homeostasis, were not clearly demonstrated in this experiment. In addition, there was no dose response concordance between the effects on thyroid homeostasis and thyroid tumor formation. Therefore, the CARC concluded that the available data do not fully support the proposed MOA.

Classification and Quantification of Carcinogenic Potential

In accordance with the EPA Final *Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified orthosulfamuron as **"Suggestive Evidence of Carcinogenic Potential".** This was based on the following weight-of-evidence considerations: (i) There was a treatment-related increase in thyroid follicular cell tumors (adenoma driven) in Han Wistar rats, males only, at 500 and 1000 mg/kg/day (limit dose). No treatment-related tumors were seen in female

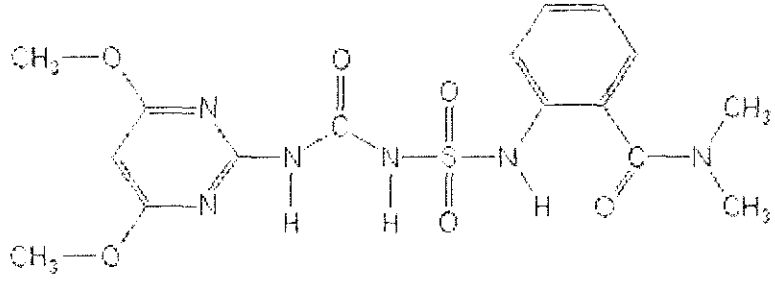
rats. Male and female rats were tested at a dose that was considered adequate to assess carcinogenicity; (ii) No treatment-related tumors were seen in male or female CD-1 mice when tested at the limit dose, which was considered adequate to assess carcinogenicity; (iii)There is no mutagenicity concern; (iv) While the registrant's proposed antithyroid mode of action for thyroid follicular cell tumors is plausible, the available data are insufficient to delineate the sequence of key events leading to tumor formation, and therefore, do not support the proposed mode of action. Linear quantification of carcinogenic potential is not required. The NOAEL and LOAEL selected for the cRfD are based on thyroid toxicity observed at doses lower than the thyroid follicular cell tumor response. Thus, the cRfD is considered protective of the cancer effects.

I. INTRODUCTION

On September 20, 2006 the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Orthosulfamuron.

II. BACKGROUND

Chemical Name:	Orthosulfamuron
IUPAC Name:	1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl)phenylsulfamoyl]urea
Other Name:	2-[[[[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]amino]-*N,N*-dimethylbenzamide
CAS Registry No.:	213464-77-8
PC Code:	108209
Structure:	



Orthosulfamuron (1-(4,6-dimethoxypyrimidin-3[2-(dimethylcarbamoyl) phenylsulfamoyl] urea) is a systemic herbicide belonging to the sulfamoylurea class of chemicals. It is being proposed for control of broadleaf weeds and sedges in rice. The mode of action for orthosulfamuron is through inhibition of the plant enzyme acetolactate synthase, which is also known as acetohydroxy acid synthase. Inhibition of this enzyme blocks branch-chain amino acid biosynthesis of valine, leucine, and isoleucine involved in plant growth processes leading to death of the plant.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study in Han Wistar Rats

Reference: Combined Carcinogenicity and Toxicity Study by Dietary Administration to Han Wistar Rats for 104 Weeks (2004). Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England. Laboratory Project No. A2/05/05/02, AGR/131/033063, AGR131. July 20, 2004. MRID 46578913.

A. Experimental Design

Orthosulfamuron (IR5878; 98.6-98.8% a.i.; Batch Nos.: FCF/T/191-01 and G009/02) was administered in the diet to 70 Han Wistar (HsdBrl Han:Wist) rats /sex/dose at nominal concentrations of 0, 1, 5, 500, or 1000 mg/kg/day for up to 2 years. Twenty rats/sex/dose were sacrificed at Week 52, and the remaining survivors were sacrificed at Week 104.

B. Discussion of Survival and Tumor Data

Survival Analysis

TOXICITY PHASE

One 500 mg/kg/day female rat was killed in *extremis* during the first 52 weeks (week 20) of treatment. Histopathological examination indicated hepatocyte torsion, necrosis, and severe congestion; this death was considered unrelated to treatment.

CARCINOGENICITY PHASE

There were no statistically significant incremental changes in mortality with increasing doses of orthosulfamuron in male rats (Memo, L. Brunsman, 8/30/06, TXR# 0054345). A total of 54 males and 66 females assigned to the carcinogenicity phase died or were sacrificed. The overall group distribution of these deaths was not affected by treatment. Survival in both sexes met the guideline requirements of 50% at week 78 and 25% at week 104.

Tumor Analyses

Males
Male rats had statistically significant trends in thyroid follicular cell adenomas, and adenomas and carcinomas combined, both at $p < 0.01$. There were statistically significant pair-wise comparisons of the 500 mg/kg/day dose group with the controls for thyroid follicular cell adenomas, and adenomas and carcinomas combined, both at $p < 0.05$. There were also statistically significant pair-wise comparisons of the 1000 mg/kg/day dose group with the controls for thyroid follicular cell adenomas, and adenomas and carcinomas combined, both at $p < 0.01$. The statistical analyses of the tumors in male rats were based upon Fisher's Exact Test for pair-wise comparisons and the *ad hoc* Exact Test for trend since there were no statistically significant trends for mortality. (Table 1, Memo, L. Brunsman, 8/30/06, TXR# 0054345).

The historical control data for thyroid follicular cell adenoma in males, provided by the Registrant, included data from 10 studies (50-60 animals/study). The study dates ranged from July 2000-September 2002 and control rats were tested for approximately 104 weeks. Out of 10 studies, 9 of these studies had adenomas. The percent affected ranged from 0%-12.5%. Historical control data were also obtained from Charles River Laboratories (Giknis and Clifford, 2001). In male Wistar Hans control rats, tested approximately 104 weeks, data were taken from 10 studies initiated prior to 1999. Of these 10 studies, all had adenomas. The percent affected ranged from 1.67-12.73%. Carcinomas were present in 7 out of 10 studies. The percent affected ranged from 1.67-3.64%.

Females
There were no treatment-related tumors observed in female rats.

Table 1. Orthosulfamuron – Han Wistar Rat Study (MRID 46578913)

Male Thyroid Follicular Cell Tumor Rates[+] and Fisher's Exact Test and Exact Trend Test Results

	Dose (mg/kg/day)				
	0	1	5	500	1000
Adenomas (%)	1/50 (2)	2/50 (4)	1/50 (2)	7[a]/50 (14)	10/49 (20)
p =	0.00006**	0.50000	0.75253	0.02972*	0.00349**
Carcinomas (%)	0/50 (0)	1/50 (2)	1[b]/50 (2)	0/50 (0)	0/49 (0)
p =	0.3223	0.5000	0.5000	1.0000	1.0000
Combined (%)	1/50 (2)	3/50 (6)	2/50 (4)	7/50 (14)	10/49 (20)
p =	0.00030**	0.30865	0.50000	0.02972*	0.00349**

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.
[a]First adenoma observed at week 70, dose 500 mg/kg/day.
[b]First carcinoma observed at week 91, dose 5 mg/kg/day.

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 controls (Registrant)**: thyroid follicular cell adenoma, range = 0%-12.5%**
Historical controls (Charles River)**: thyroid follicular cell adenoma, range = 1.67-12.73%**
thyroid follicular cell carcinomas, range= 1.67-3.64%

C. Non-Neoplastic Lesions in Han Wistar Rats

The non-neoplastic lesions in male and female rats treated with orthosulfamuron are presented in Tables 2 and 3. In a combined chronic toxicity/carcinogenicity study, after 52 weeks (toxicity phase), increased ($p \leq 0.01$) incidences of minimal to moderate centrilobular hepatocyte vacuolation were observed in the ≥500 mg/kg/day males (50-95% treated vs 0% controls) and minimal to moderate centrilobular hepatocyte hypertrophy was observed in the ≥500 mg/kg/day males (60-75% vs 10%) and 1000 mg/kg/day females (60% vs 0%). Additionally at Week 52, increased incidence ($p \leq 0.05$) in pancreatic acinar cell vacuolation was observed in the 1000 mg/kg/day males (95% treated vs 45% controls); however, other indications of toxicity were not evident, and an adverse effect at 104 weeks was also not substantiated.

In the carcinogenicity phase, increased ($p \leq 0.05$) incidences of the following findings (% treated vs % controls) were observed in the liver: (i) minimal to marked centrilobular hepatocyte vacuolation in the ≥500 mg/kg/day males (62-80% vs 30%); (ii) slight centrilobular hepatocyte hypertrophy in the 1000 mg/kg/day males (42% vs 6%); (iii) minimal to slight cystic degeneration in the 1000 mg/kg/day males (16% vs 0%); and (iv) slight to moderate focal sinusoidal dilatation in the 1000 mg/kg/day females (12% vs 0%). In the thyroid, increased incidences of minimal to marked cystic follicular cell hyperplasia (20% treated vs 4% controls; $p \leq 0.05$) were noted in the 1000 mg/kg/day males, and increased incidences of minimal follicular cell hypertrophy were observed in the ≥500 mg/kg/day males (42% each treated vs 24% control). An increased (NS) incidence in slight to moderate chronic progressive nephropathy of the kidney was observed in the ≥500 mg/kg/day males (46-52% treated vs 34% controls). Increased ($p \leq 0.05$) incidences in the following kidney lesions were observed (% treated vs % controls) in females: (i) slight to marked chronic progressive nephropathy at 1000 mg/kg/day (52% vs 24%); (ii) minimal to marked pelvic/papillary epithelium hyperplasia at ≥500 mg/kg/day (88-92% vs 70%); and (iii) minimal to marked papillary/pelvic epithelium mineralization at ≥5 mg/kg/day (88-94% vs 74%; NS at 5 and 500 mg/kg/day). An increased ($p \leq 0.05$) incidence of minimal to moderate hemosiderosis was observed in the spleen of the ≥500 mg/kg/day females (86-92% treated vs 66% controls).

Additionally, increased incidence of peri-islet pigment in the pancreas (22% treated vs 6% controls; $p \leq 0.05$) was noted in the 1000 mg/kg/day males; however, this isolated finding was considered incidental. Increased incidences of other findings in the treated groups relative to controls were minor and/or not corroborated by other clinical or pathological findings.

Table 2. Non-Neoplastic Histopathological Findings in Male and Female Rats Treated With *Orthosulfamuron in the Diet for up to 52 Weeks (toxicity phase).*

Microscopic lesion		Dose (mg/kg/day)				
		0	1	5	500	1000
Males						
Liver	Hepatocyte vacuolation, centrilobular (total)	0 (0)	0 (0)	0 (0)	10** (50)	19** (95)
	Minimal	0	0	0	10	5
	Slight	0	0	0	0	9
	Moderate	0	0	0	0	5
	Hepatocyte hypertrophy, centrilobular (total)	2 (10)	5 (25)	2 (10)	12** (60)	15** (75)
	Minimal	2	5	2	11	0
	Slight	0	0	0	1	14
	Moderate	0	0	0	0	1
Females						
Liver	Hepatocyte hypertrophy, centrilobular (total)	0 (0)	0 (0)	0 (0)	0 (0)	12** (60)
	Minimal	0	0	0	0	11
	Slight	0	0	0	0	1

a Data were obtained from Table 29F on pages 257-273 and pages 1549-2131 of MRID 46578913.

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

Table 3. Non-Neoplastic Histopathological Findings in Male Rats Treated With Orthosulfamuron in *the Diet for up to 104 Weeks (carcinogenicity phase).*

Microscopic lesion		Dose (mg/kg/day)				
		0	**1**	**5**	**500**	**1000**
Liver	Hepatocyte vacuolation, centrilobular (total)	15/50 (30)	5/50* (10)	4/50** (8)	31/50** (62)	40/50** (80)
	Minimal	11	4	3	16	6
	Slight	4	1	1	12	28
	Moderate	0	0	0	2	6
	Marked	0	0	0	1	0
	Hepatocyte hypertrophy, centrilobular, slight (total)	3/50 (6)	4/50 (8)	3/50 (6)	8/50 (16)	21/50** (42)
	Cystic degeneration (total)	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)	8/50** (16)
	Minimal	0	0	0	0	3
	Slight	0	0	0	0	5
Thyroid	Cystic follicular cell hyperplasia	2/50 (4)	0/50 (0)	4/50 (8)	5/50 (10)	10/49* (20)
	Minimal	1	0	1	1	1
	Slight	0	0	1	2	5
	Moderate	1	0	2	2	2
	marked	0	0	0	0	2
	Follicular cell hypertrophy, minimal (total)	12/50 (24)	11/50 (22)	16/50 (32)	21/50 (42)	21/49 (42)
Kidney	Chronic progressive nephropathy (total)	17/50 (34)	12/50 (24)	7/50* (14)	26/50 (52)	23/50 (46)
	slight	16	11	5	24	21
	moderate	1	0	1	2	2
	marked	0	1	1	0	0

a Data were obtained from Table 29F on pages 257-273 and pages 1549-2131 of MRID 46578913.

* Significantly different from controls; $p \leq 0.05$

** Significantly different from controls; $p \leq 0.01$

Adequacy of the Dosing for Assessment of Carcinogenicity

The CARC concluded that dosing of male and female rats at the high dose of 1000 mg/kg/day was adequate, but not excessive, to assess the carcinogenicity of orthosulfamuron because the study was conducted at the limit dose. In addition, decreased body weight gains (32-38% during the second year; 12-20% over the entire study) in both sexes and slight hepatotoxicity and nephrotoxicity were observed at 1000 mg/kg/day.

There were no significant treatment-related effects on mortality. One 500 mg/kg/day female died during the toxicity phase of the study. In the carcinogenicity phase animals, survival was 64-84% for all groups, and response was unrelated to dose. Thus, survival exceeded guideline requirements of 50% at Week 78 and 25% at Week 104 in both sexes.

At week 52, relative liver weights were increased ($p \leq 0.01$) in both sexes at 500 (↑9-11%) and 1000 (↑14-22%) mg/kg/day. Additionally in the 1000 mg/kg/day males, increases ($p \leq 0.01$) were observed in absolute liver weights (↑20%) and relative kidney weights (↑7%). There were also increased ($p \leq 0.01$) incidences of minimal to moderate centrilobular hepatocyte vacuolation observed in the ≥500 mg/kg/day males (50-95% treated vs 0% controls) and minimal to moderate centrilobular hepatocyte hypertrophy in the ≥500 mg/kg/day males (60-75% vs 10%) and 1000 mg/kg/day females (60% vs 0%).

During the second year (Weeks 52-104) of treatment at ≥500 mg/kg/day, body weight gains were significantly ($p \leq 0.05$) decreased in both sexes (↓24-29%, 500 mg/kg/day; not significant [NS] in the 500 mg/kg/day males; ↓32-38%, 1000 mg/kg/day), resulting in decreased ($p \leq 0.05$) overall (Weeks 0-104) body weight gains of 11-14% at 500 and 12-20% at 1000 mg/kg/day. Relative kidney weights were increased ($p \leq 0.01$) by 11-14%, and an increased (NS) incidence in slight to moderate chronic progressive nephropathy of the kidney (46-52% treated vs 34% controls) was observed in males. In females, increased ($p \leq 0.05$) incidences (% treated vs % controls) of minimal to marked pelvic/papillary epithelium hyperplasia (88-92% vs 70%) and minimal to marked papillary/pelvic epithelium mineralization (90-94% vs 74%; NS at 500 mg/kg/day) were noted.

At 2 years, the following findings were noted in males: i) increased incidence of dark area(s) on the liver; ii) increased absolute liver weights; iii) increased incidence of slight centrilobular hepatocyte hypertrophy; and iv) increased incidence of minimal to slight cystic degeneration. In the females, the following findings were observed: i) increased relative liver weights; ii) increased incidence of slight to moderate focal sinusoidal dilatation; iii) increased blood urea; iv) increased relative kidney weights; and v) increased incidence of slight to marked chronic progressive nephropathy.

2. Carcinogenicity Study in CD-1 Mice

Reference: Carcinogenicity Study by Dietary Administration to CD-1® Mice for 78 Weeks (2002). Huntingdon Life Sciences Ltd., Huntingdon, Cambridgeshire, England. Laboratory Project No. AGR/130. December 22, 2003. MRID 46578912

A. Experimental Design

Orthosulfamuron (IR5878; 98.0% a.i.; Batch #: FCF/T/172-00 (ex 20525/03/8)] was administered in the diet to 50 Crl:CD-1™ (ICR)BR mice/sex/dose at nominal concentrations of 0, 100, 500, or 1000 mg/kg/day for up to 78 weeks.

B. Discussion of Survival and Tumor Data

Survival Analyses

There were no treatment-related effects observed on mortality. Survival in all groups was 70-88% at Week 65, and 58-76% at Week 78, exceeding guideline requirements of 50% at Week 65 and 25% at Week 78.

Tumor Analyses

There were no treatment-related tumors observed in male or female mice.

C. Non-Neoplastic Lesions in CD-1 Mice

The non-neoplastic lesions observed in male and female mice treated with orthosulfamuron are presented in Table 4. There were increased ($p \leq 0.001$) incidences of slight to moderate centrilobular hepatocyte hypertrophy at ≥500 mg/kg/day (48-68%) compared to slight hypertrophy in controls (8%). Increased ($p \leq 0.05$) incidences of slight to marked centrilobular hepatocyte vacuolation was observed at 1000 mg/kg/day (50%), and slight to moderate vacuolation at 500 mg/kg/day (38%); both compared to slight to moderate vacuolation in controls (18%). Similar changes were not observed in females. Increased ($p \leq 0.01$) splenic white pulp cellularity was noted in the 1000 mg/kg/day females (28%) compared to controls (3%); however, this effect was no longer significant when animals that died prior to scheduled termination were included. No other treatment-related adverse effects were observed during non-neoplastic microscopic pathology.

TABLE 4: Non-Neoplastic Lesions in Mice after up to 78 weeks of treatment with orthosulfamuron in the diet

Dose (mg/kg/day)		0	100	500	1000
Centrilobular hepatocyte hypertrophy -	Total	8%	20%	48% ***	68% ***
	Slight	8%	18%	40%	54%
	Moderate	0	2%	8%	14%
Centrilobular hepatocyte vacuolation -	Total	18%	24%	38% *	50% **
	Slight	12%	18%	28%	24%
	Moderate	6%	6%	10%	24%
	Marked	0	0	0	2%

a Data were obtained from Text table 3 on page 28 and Table 10 F on page 147 of the study report. Percent difference from controls was calculated by the reviewers, $n=50$.
* Significantly different from controls, $p \leq 0.05$.
** Significantly different from controls, $p \leq 0.01$.
*** Significantly different from controls, $p \leq 0.001$.

C. Adequacy of Dosing for Assessment of Carcinogenicity

The CARC concluded that dosing of male and female mice at the high dose of 1000 mg/kg/day, was adequate, but not excessive, to assess the carcinogenicity of orthosulfamuron because the study was conducted at the limit dose. Increased liver weights and increased incidence of centrilobular hepatocyte hypertrophy and centrilobular hepatocyte vacuolation were observed in males. Although the high dose of 1000 mg/kg/day in this mouse study did not result in systemic toxicity in females, the study was adequate because the limit dose was tested.

There were no significant treatment-related effects on mortality. At the doses tested, the number of surviving males and females in all groups met the minimal survival requirements of 50% at Week 65 and 25% at Week 78.

Absolute (↑12%, $p \leq 0.05$) and relative to body (↑14%, $p \leq 0.05$) liver weights were increased in the 1000 mg/kg/day males after 78 weeks of treatment when compared with controls. The following lesions were observed in the centrilobular hepatocytes of the males: increased ($p \leq 0.001$) incidence of slight to moderate hypertrophy at ≥500 mg/kg/day (48-68%) compared to slight in controls (8%); and increased ($p \leq 0.05$) incidence of slight to marked vacuolation at 1000 mg/kg/day (50%), and slight to moderate vacuolation at 500 mg/kg/day (38%), both compared to slight to moderate in controls (18%). Similar changes were not observed in females.

IV. TOXICOLOGY

1. Metabolism

EXECUTIVE SUMMARY: In a rat metabolism study (MRIDs 46578905 through 46578910), [^{14}C-U-phenyl] IR5878 (Lot No. 182) or [^{14}C-5-pyrimidinyl] IR5878 (Lot No. 180) in 0.5% aqueous carboxymethycellulose (radiochemical purity >97%) was administered by gavage to Sprague Dawley rats. In the preliminary study, 2 rats/sex received a single 250 mg/kg dose. In the main study, 4 rats/sex/dose received a single dose of 5 or 1000 mg/kg or 14 daily doses at 5 mg/kg (non-radioactive) followed by a single radioactive dose (5 mg/kg) on day 15. Additionally, a biliary excretion study was performed where 4 males and 7 females received a single dose at 5 mg/kg. Pharmacokinetic analyses of the absorption and distribution were performed, including blood kinetics, along with identification of the metabolites in the excreta.

Absorption was rapid in all groups, regardless of sex, dose, or number of doses. T_{max} values were 12 min for the 5 mg/kg repeated dose group, 24 min-1 h for the single 5 mg/kg dose group, and 1-4 h for the single 1000 mg/kg dose group. Following a single 5 mg/kg dose of [^{14}C-U-phenyl] IR5878, 76-82% of the dose was absorbed and found in the urine/cage wash, bile, and carcass, indicating extensive absorption. The half-life (8-48 h) was similar regardless of sex, dose, or number of doses (8.9-13.3 h), with the exception of the females treated with a single 5 mg/kg dose of [^{14}C-5-pyrimidinyl] IR5878 (16.7 h).

Within 12 h of administration of the radiolabeled dose (5 or 1000 mg/kg single dose or multiple 5 mg/kg doses), approximately half of the dose was excreted, and excretion was almost complete at 72 h post-dose.

At 72 h post dose, overall recovery of the radioactive dose from both sexes was 92-100%. The majority of the dose was recovered in the feces (43-73%); 18-46% of the dose was found in the urine; and cage wash accounted for 1-5% dose. Minimal radioactivity was detected in the carcass and GI tract (<0.8% dose). In a preliminary study, <0.02% of the radioactive dose was isolated in the expired air; therefore, this route of excretion was not analyzed. A difference in the excretion profile was generally not noted based on sex, dose, or number of doses. Regardless of sex, dose, or number of doses, the distribution of radioactivity in tissues was similar. Comparison of the concentrations of radioactivity in tissues on the basis of radiolabel was not possible due to differing sampling times and/or differing T_{max} while a time course of tissue distribution was not performed. Excluding the GI tract, concentrations of radioactivity were highest in the liver, kidney, lung, and whole blood, with the lung having the lowest concentrations. At 5 mg/kg (single or multiple doses), these tissue concentrations were 1.74-23.83 µg equiv./g vs 2.41-5.10 µg equiv./g in whole blood. At 1000 mg/kg in all treated rats, these tissue concentrations were 161-435 µg equiv./g vs 305-495 µg equiv./g in whole blood. As relatively little radioactivity remained in the carcass at 72 h post-dose (≤0.70% dose), bioaccumulation is not suspected under the test conditions.

HPLC and HPLC-MS analyses were used to identify parent and a total of 10 metabolites in excreta from rats treated with [^{14}C] IR5878. Six to 7 metabolites were identified after treatment with each radiolabeled compound, and 3 of these metabolites were common to treatment with

both radiolabeled compounds. Parent and identified metabolites in excreta accounted for 71-86% dose in all animals, and overall recovery was 95-99% dose. Unidentified compounds accounted for 1-16% dose, but no single compound accounted for ≥5% dose.

The parent was found in 5 mg/kg animals (single and multiple doses) at 1-6% dose and in 1000 mg/kg animals at 33-56% dose. The predominant metabolite was 1-(4-methoxy-6-hydroxypyrimidin-2-yl)-3-[2-(dimethylcarbamoyl)phenylsulfamoyl]urea (O-desm IR5878). It was found at 53-64% dose in all animals treated at 5 mg/kg and at 14-20% dose in all animals treated at 1000 mg/kg. This compound was found in similar quantities in the urine and feces. 2-Sulfoamino-N,N-dimethylbenzamide (DBS acid) was a primary metabolite in all animals treated with [^{14}C-U-phenyl] IR5878 and was found at 8-12% dose. This compound was found primarily in the feces. In all animals treated with [^{14}C-5-pyrimidinyl] IR5878, a fraction was isolated (primarily in feces) that contained (4,6-dimethoxy-5-O-glucuronidyl pyrimidin-2-yl)urea (Pyr-O-Glucur DOP urea) and 1-(4,6-dimethoxy-5-O-glucuronidyl pyrimidin-2-yl)-3-[2-(dimethylcarbamoyl)phenylsulfamoyl]urea (Pyr-O-Glucur IR5878). This fraction represented 9-18% dose. Additionally, 1-(4,6-dimethoxypyrimidin-2-yl)-3-[2-(methylcarbamoyl)phenyl-sulfamoyl]urea (N-desm IR5878) was found at 5-8% dose in the urine of animals treated with 1000 mg/kg [^{14}C-5-pyrimidinyl] IR5878. All other identified metabolites each accounted for <5% dose. Identification of IR5878 metabolites indicates that metabolism is mainly occurring through O- and/or N-demethylations. Additionally, hydrolytic cleavage of the sulfamoylurea linkage yields DOP urea, and hydroxylation of the pyrimidinyl ring occurs followed by glucuronic acid or sulfate conjugation.

The metabolic profile of the liver, kidney, and bile was also evaluated. In the liver and kidneys of all animals treated with [^{14}C-U-phenyl] IR5878, the parent and O-desm IR5878 were found in the highest concentrations. In the liver and kidneys of all animals treated with [^{14}C-5-pyrimidinyl] IR5878, O-desm IR5878 and an unidentified fraction were generally found in the highest concentrations, as well as 2-amino-N,N-dimethylbenzamide (DB amine) in the male kidney. In the bile, O-desm IR5878 and an unidentified fraction were found in the highest concentration. Other identified compounds (same as found in the excreta) were not detected in the liver, kidney, or bile or were generally found at relatively low concentrations.

This metabolism study in the rat is classified **acceptable/guideline** and satisfies the guideline requirement for a Tier 1 metabolism study [OPPTS 870.7485, OPP 85-1] in rats.

2. Mutagenicity

Orthosulfamuron (IR5878; parent compound)

Orthosulfamuron (IR5878) was tested in four genetic toxicology studies. The results indicate that orthosulfamuron is not mutagenic in bacteria or cultured mammalian cells. It is also not clastogenic or aneugenic *in vivo* in a bone marrow mouse micronucleus assay, or *in vitro* in a chromosome aberration assay.

Orthosulfamuron Metabolites (IR7825, IR7863, and IR8181)

Several metabolites of orthosulfamuron (IR7825, IR7863, and IR8181) were tested in genetic toxicology studies. The results indicate that the three metabolites are not mutagenic in bacteria or cultured mammalian cells. The metabolite IR 8181 is not clastogenic or aneugenic *in vivo* in a bone marrow mouse micronucleus assay (other metabolites were not tested). IR7825 and IR7863 were not clastogenic or aneugenic in an *in vitro* chromosome assay; however, IR8181 exposure resulted in evidence of chromosome aberrations induced over background in the presence and absence of S-9 activation.

GENE MUTATIONS

I. Orthosulfamuron (IR5878; parent compound) was not mutagenic in independently conducted *Salmonella typhimurium* and *Escherichia coli* mammalian microsome reverse gene mutation assays (MRID 46219034) up to the limit dose (5000 µg/plate +/- S9). In addition, three metabolites (IR7825, IR7863, and IR8181) were not mutagenic in independently conducted *Salmonella typhimurium* mammalian reverse gene mutation assays (MRID 46578916, 46578919, and 46578923) tested up to the limit dose (5000 µg/plate +/- S9). Cytotoxicity, as indicated by a reduction in revertant colonies, was, however, seen at 5000 µg/plate +/- S9 in the majority of strains treated with IR 7825 (MRID 46578916). The studies are acceptable.

II. The parent compound (MRID 46219036) and all three metabolites (MRID, 46578914, 46578920, and 46578925) were non-mutagenic in mouse lymphoma L5178Y cell forward gene mutation assays up to the limit dose or the limit of solubility. The studies are acceptable.

CHROMOSOME ABERRATIONS

III. Orthosulfamuron (IR 5878; parent compound) and two metabolites (IR7863 and IR 7825) did not produce a significant increase in either structural or numerical aberrations at doses up to the limit dose or the limit of solubility in human lymphocyte cytogenetic assays (MRID 46219035, 46578921, and 46578917, respectively). However, in another human lymphocyte cytogenetics assay with IR8181 (MRID 46578924), the metabolite induced increases (exceeding historical control range of 0-4%) in the mean percent aberrant cells (excluding gaps) at 1250 and 2500 µg/mL (+S9) and at ≥1250 µg/mL (-S9). At these concentrations, relative mitotic indices were ≥ 50% of the control. The studies are acceptable.

IV. In *in vivo* mice micronucleus assays, the parent compound (MRID 46219037), and the metabolite IR8181(MRID 46578926), did not induce a clastogenic or aneugenic response in bone marrow cells harvested from male mice administered a single dose or doses up to the limit dose of 2,000 mg/kg. The studies are acceptable.

CONCLUSION:

The overall results indicate that neither the parent compound nor metabolites IR7863 or IR7825 are mutagenic. In contrast, metabolite IR8181 was positive for the induction of structural chromosome aberrations at concentrations that were minimally cytotoxic. However, there is no concern for mutagenicity at this time because the evidence of *in vitro* mutagenicity is not expressed in the whole animal.

3. Structure-Activity Relationship

The closest structural analog to orthosulfamuron is cyclosulfamuron. Based on the structural similarities, it is likely that cyclosulfamuron shares the same properties as orthosulfamuron. Cyclosulfamuron is not currently registered by the EPA; therefore, toxicology data are not available at this time.

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity

90-Day Oral Toxicity - Rat (870.3100)

EXECUTIVE SUMMARY: In a 90-day subchronic oral toxicity study (MRID 46260103), IR5878 (98.0% a.i., Batch No. FCF/T/172-00 (ex 20525/03/8) was administered to ten Han Wistar rats/sex/dose in the diet at dose levels of 0, 250, 1500, and 9000 ppm (equivalent to 0, 19, 113, and 706 mg/kg bw/day, respectively, for males and to 0, 22, 131, and 773 mg/kg bw/day, respectively, for females). Concurrently, a recovery group of five Han Wistar rats/sex/dose were administered either 0 or 9000 ppm (equivalent to 0 or 706 mg/kg bw/day, respectively, for males and to 0 or 773 mg/kg bw/day, respectively, for females) during the 90-day study period and were then maintained for an additional four weeks on the control diet. There were no compound-related effects on mortality, body weights, body weight gains, food consumption, neurological observations and measurements, hematology, clinical chemistry, or gross pathology. Compared to controls, an increase in dorsal hair loss was seen in females, but this finding is common. Other treatment-related effects (transient increases in liver weight and hepatocellular hypertrophy in high-dose males compared to controls) indicate a minimal, adaptive response in the liver following exposure to IR5878 that is not considered adverse.

The LOAEL was not identified in this study (>706 mg/kg/day for males and >773 mg/kg/day for females). The NOAEL is the highest dose tested in this study (9000 ppm), which was equivalent to 706 mg/kg/day for males and 773 mg/kg/day for females.

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the rat.

90-Day Oral Toxicity - Mouse (870.3100)

EXECUTIVE SUMMARY: In a 90-day subchronic oral toxicity study (MRID 46260102), orthosulfamuron (IR5878; 98.0% a.i., Batch No. FCF/T/172-00 (ex 20525/03/8) was administered to ten CD-1 mice/sex/dose in the diet at dose levels of 0, 250, 1250, and 6000 ppm (equivalent to 0, 36, 187, and 865 mg/kg bw/day, respectively, for males and to 0, 47, 228, and 1096 mg/kg bw/day, respectively, for females).

There were no compound-related effects on clinical signs, mortality, body weights, clinical chemistry, gross pathology, or histopathology. Compared to controls, slight decreases in food consumption, MCH, and MCV in high-dose females and slight decreases in the lymphocyte count of high-dose males were noted, but these changes were not biologically significant.

The LOAEL was not identified in this study (>865 mg/kg/day for male mice and >1096 mg/kg/day for females). The NOAEL is the highest dose tested in this study (6000 ppm), which was equivalent to 865 mg/kg/day for male mice and 1096 mg/kg/day for females. Dosing in this study is considered adequate because the highest dose tested is sufficiently close to the limit dose of 1000 mg/kg/day.

This study is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in the mouse.

b) Chronic Toxicity

Combined Chronic Toxicity/Carcinogenicity - Rat (870.4300)

EXECUTIVE SUMMARY - In this combined chronic toxicity/carcinogenicity study (MRID 46578913), orthosulfamuron (IR5878; 98.6-98.8% a.i.; Batch Nos.: FCF/T/191-01 and G009/02) was administered in the diet to 70 Han Wistar (HsdBrl Han:Wist) rats /sex/dose at nominal concentrations of 0, 1, 5, 500, or 1000 mg/kg/day for up to 2 years. Twenty rats/sex/dose were sacrificed at Week 52, and the remaining survivors were sacrificed at Week 104.

No treatment-related effects were observed on mortality, functional observational battery findings, food consumption, food efficiency, ophthalmoscopic examination, hematology, or urinalysis.

At 500 mg/kg/day and above, body weight gains were decreased ($p<=0.05$) in both sexes during the second year (Weeks 52-104) of treatment by 24-38% (not significant [NS] in the 500 mg/kg/day males), resulting in decreased ($p<=0.05$) overall (Weeks 0-104) body weight gains (decr. 11-20%).

Hepatotoxicity was observed at 500 mg/kg/day and above. At 1 year, relative to body liver weights were increased ($p<=0.01$) in both sexes by 9-22%. In the males, increased ($p<=0.01$) incidences were noted in minimal to moderate centrilobular hepatocyte

vacuolation (50-95% treated vs 0% controls) and minimal to moderate centrilobular hepatocyte hypertrophy (60-75% vs 10%). At 2 years in the males, relative to body liver weights were increased ($p \leq 0.01$) by 9-23%, and increased ($p \leq 0.05$) incidence of minimal to marked centrilobular hepatocyte vacuolation was observed (62-80% treated vs 30% controls).

In the thyroid after 104 weeks, increased incidences of minimal to marked cystic follicular cell hyperplasia (20% treated vs 4% controls; $p \leq 0.05$) were noted in the 1000 mg/kg/day males, and increased incidences of minimal follicular cell hypertrophy were observed in the ≥500 mg/kg/day males (42% each treated vs 24% control).

Nephrotoxicity was observed at 500 mg/kg/day and above. In the carcinogenicity phase animals, incidences of perigenital yellow staining were generally increased in the males from Week 27 to termination (2-9%), and in the females from Week 32 to termination (2-24%), compared to 0 controls. At 2 years, relative kidney weights were increased ($p \leq 0.01$) by 11-14%, and an increased (NS) incidence in slight to moderate chronic progressive nephropathy of the kidney (46-52% treated vs 34% controls) was observed in the males. Additionally in the females, increased ($p \leq 0.05$) incidences (% treated vs % controls) of minimal to marked pelvic/papillary epithelium hyperplasia (88-92% vs 70%) and minimal to marked papillary/pelvic epithelium mineralization (90-94% vs 74%; NS at 500 mg/kg/day) were noted.

Additionally at 1000 mg/kg/day, increased perigenital yellow staining was noted from Week 66 to termination in the carcinogenicity phase males, from Week 3 to termination in the carcinogenicity phase females, and from Week 11 to termination in the toxicity phase females. At 1 year, increased absolute liver weights and relative kidney weights were observed in the males. At 2 years, the following findings were noted in the males: i) increased incidence of dark area(s) on the liver; ii) increased absolute liver weights; iii) increased incidence of slight centrilobular hepatocyte hypertrophy; and iv) increased incidence of minimal to slight cystic degeneration. In the females, the following findings were observed: i) increased relative liver weights; ii) increased incidence of slight to moderate focal sinusoidal dilatation; iii) increased blood urea; iv) increased relative kidney weights; and v) increased incidence of slight to marked chronic progressive nephropathy.

The LOAEL is 500 mg/kg/day, based on decreased body weight gains, slight hepatotoxicity and nephrotoxicity in both sexes and thyroid effects in males. The NOAEL is 5 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4300; OECD 453) for a combined chronic toxicity/carcinogenicity study in rats.

Carcinogenicity Study - Mouse (870.4200b)

EXECUTIVE SUMMARY - In a carcinogenicity study (MRID 46578912), 50 Crl:CD-1™ (ICR)BR mice/sex/dose were exposed to orthosulfamuron [IR5878; 98.0% a.i.; Batch #: FCF/T/172-00 (ex 20525/03/8)] in the diet at nominal concentrations of 0, 100, 500, or 1000 mg/kg/day for up to 78 weeks.

No adverse treatment-related effects were observed on clinical signs, mortality, body weights, body weight gains, food consumption or food conversion efficiency, hematology, or gross pathology.

Absolute (incr. 12%, $p \leq 0.05$) and relative to body (incr. 14%, $p \leq 0.05$) liver weights were increased in the 1000 mg/kg/day males after 78 weeks of treatment when compared with controls. An increased ($p \leq 0.001$) incidence of slight to moderate centrilobular hepatocyte hypertrophy was observed at ≥ 500 mg/kg/day (48-68%) compared to slight hypertrophy in controls (8%). Also, an increased ($p \leq 0.05$) incidence of slight to marked liver vacuolation was observed at 1000 mg/kg/day (50%), and slight to moderate liver vacuolation at 500 mg/kg/day (38%), both compared to slight to moderate in controls (18%). Similar changes were not observed in females. It was stated that the observed increased incidence of centrilobular hepatocyte vacuolation, suggesting an effect on fat metabolism, in 500 and 1000 mg/kg/day compound-treated males was also observed in the corresponding rat carcinogenicity study MRID 46578913 (Huntingdon Life Sciences Report Number AGR 131/033063) with this test compound.

The LOAEL is 500 mg/kg/day, based on increased incidences of centrilobular hepatocyte hypertrophy and centrilobular hepatocyte vacuolation in males. The NOAEL is 100 mg/kg/day.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.4200b; OECD 451) for a carcinogenicity study in mice.

5. *Mode of Action*

Background

A number of chemical substances have been shown to induce thyroid follicular cell tumors in rats through a mode of action that involves perturbation of thyroid hormone homeostasis via reduction of circulating thyroid hormones (Hurley *et al.*, 1998; IARC, 1999, 2001). Homeostatic responses to low thyroid hormone concentrations result in a compensatory increase in the release of thyroid stimulating hormone (TSH) from the pituitary gland, which in turn stimulates the thyroid gland to increase thyroid hormone synthesis and release. Persistent elevation of TSH levels leads to thyroid follicular cell hypertrophy and hyperplasia, which if maintained (due to continuous exposure to the compound) can eventually lead to neoplasia. This neoplastic mode of action in rats is well accepted by the scientific community (IARC 1999; 2000; US EPA 1998). Most antithyroid pesticides operate at an extrathyroidal site by increasing

hepatic metabolism and excretion of thyroid hormone. However, a few pesticides have been shown to operate at an intrathryoidal site (for example by inhibiting hormone synthesis or release).

Investigation of the Potential Effects on Thyroid Function in Male Rats

In a non-guideline study (MRID 46578927) in rats, the effect of orthosulfamuron (IR5878; Batch# G 009/02; 98.79% a.i.) on thyroid function was investigated. Potential direct pathways (using the perchlorate discharge test) and indirect mechanisms [determined by: (i) thyroxine pharmacokinetics using ^{125}I clearance; (ii) plasma thyroid hormone levels; and (iii) organ weights and histopathology of the liver and thyroid] were examined. In the study, the test substance was administered in the diet to 28 male Han Wistar rats/dose at doses of 0, 5, and 1000 mg/kg for up to 90 days. Out of the 28 rats/group placed on study, 6 rats/group were used for each of the three categories of parameters listed above. Propylthiouracil (200 mg/kg) was included as a positive control for the perchlorate discharge test and was administered daily via oral gavage to 15 rats for the final 16 days prior to termination on Day 90. Phenobarbital (75 mg/kg) was included as a positive control for the remaining parameters and was administered daily via oral gavage to 15 rats for 14 days prior to termination of Day 90.

Registrant's Conclusion: **Induction of UDP-GT results in increased elimination of T4** (Figure 1.), which is supported by the pharmacokinetic data. At 1000 mg/kg/day, ^{125}I-T4 exhibited slightly increased clearance compared to negative controls, indicated by decreased whole blood concentrations of radioactivity and AUC_{72} values and increased systemic clearance, V_c, V_{ss}, and V_z. The positive control group responded similarly, only with a greater magnitude difference from negative controls.

The increased elimination of T4 activates the negative feedback loop to stimulate the pituitary to release TSH. In the MOA study, TSH levels were increased at 1000 mg/kg on Day 90, with an even greater increase in the phenobarbital group. **TSH acts on the thyroid follicular cells to produce T3/T4; when this process is prolonged, it results in hypertrophy, hyperplasia, and eventually, tumor formation.** Although thyroid/parathyroid weights were comparable to controls in this study, enlarged thyroids were noted in the 5 mg/kg (1/6 rats) and 1000 mg/kg (2/6 rats) compared to 0/6 negative controls and 4/6 phenobarbital treated rats. Minimal follicular cell hypertrophy was noted at 1000 mg/kg (4/6 rats) compared to negative controls (1/6 rats). In the phenobarbital group, minimal to slight follicular cell hypertrophy was observed in all (6/6) rats.

In conclusion, there was no direct effect of the test substance on the thyroid, as indicated by the perchlorate assay. The increased organ weight, hypertrophy, and induction of UDP-GT in the liver and the increased TSH and enlarged thyroids and follicular cell hypertrophy support an indirect effect of the test substance on the thyroid

CARC's Discussion

With a disruption in thyroid homeostasis, there is typically a reduction in both circulating serum T4 and T3 and a subsequent increase in TSH. In the thyroid study, there were transient decreases in concentrations of T3 observed in the 5 and 1000 mg/kg/day groups (Day 30), and no reductions in T4 concentrations. TSH levels at Day 90 in the 1000 mg/kg/day group were slightly increased (↑58%); however, TSH levels were comparable to controls at all other time points.

Agents that affect thyroid homeostasis stimulate thyroid enlargement. Common measured parameters include but are not limited to increases in thyroid weight and histological indication of cellular hypertrophy and hyperplasia. There were enlarged thyroids noted in the study at 5 and 1000 mg/kg/day, but there were no treatment-related effects observed on thyroid/parathyroid weights; liver weights were increased at 1000 mg/kg/day. At 1000 mg/kg/day, there were increased incidences of centrilobular hepatocyte hypertrophy and thyroid follicular cell hypertrophy observed. Comparatively, centrilobular hypertrophy and thyroid follicular cell hypertrophy were also observed in the combined chronic/carcinogenicity study in rats at 500 and 1000 mg/kg/day. In the chronic rat study, there were also thyroid cysts and thyroid follicular hyperplasia observed in males, as well as additional liver effects.

There were several increases in liver enzymes and activities observed in males at 1000 mg/kg/day. These included the following: (i) microsomal protein (↑32%); (ii) concentration of cytochrome P450 (↑28-69%); (iii) activity of PROD (↑2958-4020%); and (iv) activity of thyroxine UDP-GT (↑64-115%). Pharmacokinetic data in the study, revealed the following differences (not compared to negative controls: (i) decreased whole blood concentrations of radioactivity (↓4-19%); (ii) decreased AUC_{72} values (↓11%); (iii) increased systemic clearance (↑12%); (iv) increased volume of the central compartment (V_c; ↑12%); and (v) increased volume at steady state (V_{ss}; ↑9%). The increase in liver enzymes/activities and pharmacokinetic data suggests that orthosulfamuron may enhance thyroid hormone metabolism and clearance via induction of liver microsomal enzymes.

A summary table of effects in rats exposed to orthosulfamuron is presented in Table 5.

The thyroid organ weight and histological data are characteristic of increases in thyroid growth. Thus, with this information and the metabolism data, it is plausible that exposure to orthosulfamuron may cause thyroid tumors via perturbation of thyroid-pituitary functioning due to enhanced hepatic clearance of thyroxin. However, the thyroid hormone data, which are critical to delineating a sequence of key events leading to tumor formation, are inadequate. **Thus, the CARC concluded that the available data do not fully support the proposed MOA.** The following deficiencies were noted in the study:

- Alterations in thyroid hormones are typically seen at early time points, with decreases observed in circulating levels of T4 and T3 and consequent increases in TSH. It should be noted, that in general, hepatic microsomal enzyme inducers appear to affect T3 less than T4, and thus, T4 and TSH tend to be more reliable indicators of altered pituitary-

thyroid homeostasis. However, in this thyroid study, there were only small increases in TSH, seen only at Day 90, and transient decreases in T3, seen only at Day 30. Decreases in T3 were observed at 1000 mg/kg/day and similar decreases were seen at the non-tumorigenic dose of 5 mg/kg/day. Additionally, there were no decreases in T4 observed. Furthermore, the positive control (phenobarbital) did not effectively alter hormone levels and was not measured during the critical time frame where changes in thyroid hormones are expected to occur (Day 30). Suggested time points for the study are 14 days (early), 30-50 days (mid), and 90 days (late), including measurements of positive control at all time points.

- There was no dose response concordance with the tumor response observed in the chronic/carcinogenicity study in the rat. Tumors were observed at 500 and 1000 mg/kg/day, while the thyroid study investigated effects at 5 and 1000 mg/kg/day. It is recommended that 3 doses be used for the study, and that these doses correspond with the observed tumor response. In this case, 250, 500, and 1000 mg/kg/day are recommended doses for identification of a clear dose response.

It is recommended that the registrant meet with the Agency prior to conducting a repeat thyroid study.

Table 5. Comparison of Science Policy Council Mandatory Criteria for Demonstration of Thyroid-pituitary Imbalance and Effects Observed After Orthosulfamuron Exposure.

SPC criterion/	Study	Observed effect	MRID
Cellular growth	13-week investigative	Enlarged thyroids at 5 and 1000 mg/kg/day, thyroid follicular cell hypertrophy at 1000 mg/kg/day, no increase in thyroid weight or evidence of cell proliferation.	46578927
	13-week toxicity	No increase in thyroid weight, or evidence of cell proliferation	46260103
	104-week carcinogenicity	Thyroid cysts in males at 1000 mg/kg/day thyroid follicular cell hypertrophy in males at 500 and 1000 mg/kg/day, thyroid cystic follicular cell hyperplasia in males at 500, and 1000 mg/kg/day	46578913
Hormone changes	13-week investigative	Increase in TSH concentration (58%) on D90, transient decrease in T3 on D30 at 5 and 1000 mg/kg/day (not seen on D90).	46578927
	13-week toxicity	Hormones not measured	46260103
	104-week carcinogenicity	Hormones not measured	46578913
Site of action	13-week investigative	Increased liver weights and centrilobular hepatocyte hypertrophy at 1000 mg/kg/day. At 1000 mg/kg/day, there were increases in liver enzymes/activities • Microsomal protein (32%) • Cytochrome P450 (28-69%) • PROD activity (2958-4020%) • Thyroxine UDP-GT (64-115%)	46578927
	13-week toxicity	Increased liver weight and centrilobular hepatocyte hypertrophy at 706 mg/kg/day	46260103
	104-week carcinogenicity	Increased relative liver weights at 500 and 1000 mg/kg/day and absolute weights at 1000 mg/kg/day, centrilobular hepatocyte vacuolation and hypertrophy at 500 and 1000 mg/kg/day, cystic degeneration at 1000 mg/kg/day	46578913
Dose correlations	13-week investigative	Increased TSH at 1000 mg/kg/day, not seen at 5 mg/kg/day. Increased liver enzymes (P450, Microsomal) and activities (PROD, UDP-GT) at 1000 mg/kg/day, not seen at 5 mg/kg/day. Liver/thyroid effects at 1000 mg/kg/day, none seen at 5mg/kg/day.	46578927
	13-week toxicity	113 mg/kg/day-No liver effects 706 mg/kg/day-Increased liver weight and centrilobular hepatocyte hypertrophy in males.	46260103
	104-week carcinogenicity	Thyroid follicular cell adenoma at 500 and 1000 mg/kg/day, no thyroid adenoma at 5 mg/kg/day	46578913
Reversibility	13-week investigative	Reversibility not addressed in the study	465789271

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

1. Carcinogenicity

Rat

• In male Han Wistar rats, the incidences of thyroid follicular cell adenomas, carcinomas, and combined adenomas and/or carcinomas for the control, 1, 5, 500 and 1000 mg/kg/day dose groups were as follows:

Adenomas	1/50 (2%), 2/50 (4%), 1/50 (2%), 7/50 (14%), 10/49 (20%)
Carcinomas	0/50 (0), 1/50 (2%), 1/50 (2%), 0/50 (0), 0/49 (0)
Combined	1/50 (2%), 3/50 (6%), 2/50 (4%), 7/50 (14%), 10/49 (20%)

Male rats had significant positive trends ($p<0.01$) as well as significant differences in the pair-wise comparisons of the 500 mg/kg/day ($p<0.05$) and 1000 mg/kg/day ($p<0.01$) dose groups for adenomas and adenomas and carcinomas combined. The incidences of adenomas at the 500 and 1000 mg/kg/day dose groups exceeded the historical control ranges for the testing laboratory (0-12.5%) as well as for Charles River Laboratories (1.67-12.73%). Therefore, the CARC considered the thyroid follicular cell tumors (driven by adenomas) observed at 500 and 1000 mg/kg/day to be treatment-related.

• No treatment-related tumors were observed in female Han Wistar rats.

• The CARC concluded that dosing of male and female rats at the high dose of 1000 mg/kg/day was adequate, but not excessive, to assess the carcinogenicity of orthosulfamuron because the study was conducted at the limit dose. In addition, decreased body weight gains (32-38% during the second year; 12-20% over the entire study) in both sexes and slight hepatotoxicity and nephrotoxicity were observed at 1000 mg/kg/day.

Mouse

• There were no treatment related tumors observed in either male or female CD-1 mice.

• The CARC concluded that dosing of male and female mice at the high dose of 1000 mg/kg/day, was adequate, but not excessive, to assess the carcinogenicity of orthosulfamuron because the study was conducted at the limit dose. Increased liver weights and increased incidence of centrilobular hepatocyte hypertrophy and centrilobular hepatocyte vacuolation were observed in males. Although the high dose of 1000 mg/kg/day in this mouse study did not result in systemic toxicity in females, the study was adequate because the limit dose was tested.

2. Mutagenicity

The overall results indicate that neither the parent compound nor metabolites IR7863 or IR7825 are mutagenic. In contrast, metabolite IR8181 was positive for the induction of structural chromosome aberrations at concentrations that were minimally cytotoxic. However, there is no

concern for mutagenicity at this time because the evidence of *in vitro* mutagenicity is not expressed in the whole animal.

3. Structure-Activity Relationship

The very limited SAR data were not useful in the weight-of-evidence analysis.

4. Mode of Action

While it is plausible that exposure to orthosulfamuron may cause thyroid tumors via perturbation of thyroid-pituitary functioning due to enhanced hepatic clearance of thyroxin, the thyroid hormone data, which are critical to delineating a sequence of key events leading to tumor formation, are inadequate. The reduction in both circulating serum T4 and T3 and subsequent increase in TSH, as typically seen with a disruption in thyroid homeostasis, were not clearly demonstrated in this experiment. In addition, there was no dose response concordance between the effects on thyroid homeostasis and thyroid tumor formation. Therefore, the CARC concluded that the available data do not fully support the proposed MOA.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA Final *Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified orthosulfamuron as **"Suggestive Evidence of Carcinogenic Potential".** This was based on the following weight-of-evidence considerations:

(i) There was a treatment-related increase in thyroid follicular cell tumors (adenoma driven) in Han Wistar rats, males only, at 500 and 1000 mg/kg/day (limit dose). No treatment-related tumors were seen in female rats. Male and female rats were tested at a dose that was considered adequate to assess carcinogenicity;

(ii) No treatment-related tumors were seen in male or female CD-1 mice when tested at the limit dose, which was considered adequate to assess carcinogenicity;

(iii) There is no mutagenicity concern;

(iv) While the registrant's proposed antithyroid mode of action for thyroid follicular cell tumors is plausible, the available data are insufficient to delineate the sequence of key events leading to tumor formation, and therefore, do not support the proposed mode of action.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Linear quantification of carcinogenic potential is not required. The NOAEL and LOAEL selected for the cRfD are based on thyroid toxicity observed at doses lower than the thyroid follicular cell tumor response. Thus, the cRfD is considered protective of the cancer effects.

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