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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No. 0054345

MEMORANDUM

DATE: August 30, 2006

SUBJECT: **Orthosulfamuron:** Qualitative Risk Assessment Based On Male Han Wistar (HsdBrl Han:Wist) Rat Carcinogenicity Dietary Study

**P.C. Code: 108209**

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## BACKGROUND

A combined chronic toxicity/carcinogenicity study in Han Wistar rats was conducted by Huntingdon Life Sciences, Ltd., Huntingdon, Cambridgeshire, England, for ISAGRO S.p.A., Centro Uffici San Siro, Milano, Italy, and dated July 20, 2004 (Laboratory Project ID No. AGR/131/033063, MRID No. 46578913).

The study design allocated groups of 50 rats per sex to dose levels of 0, 1, 5, 500 or 1000 mg/kg/day (mean achieved doses of 0, 1.0, 5.1, 510.8 or 1026.0 for males; 0, 1.0, 5.2, 520.3 or 1046.5 for females) of Orthosulfamuron for 104 weeks. An additional 20 rats per sex per dose were designated for interim sacrifice at week 52. There were no compound-related tumors in the females so only analyses of the males are presented in this document.

## ANALYSES

### Survival Analyses

There were no statistically significant incremental changes in mortality with increasing doses of Orthosulfamuron in male rats (Table 1).

### Tumor Analyses

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 2).

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

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

| | Weeks | | | | | |
|---|---|---|---|---|---|---|
| Dose (mg/kg/day) | 1-26 | 27-52 | 52[i] | 53-78 | 79-106[f] | Total |
| 0 | 0/70 | 0/70 | 20/70 | 3/50 | 11/47 | 14/50 (28) |
| 1 | 0/70 | 0/70 | 20/70 | 6/50 | 5/44 | 11/50 (22) |
| 5 | 0/70 | 0/70 | 20/70 | 2/50 | 8/48 | 10/50 (20) |
| 500 | 0/70 | 0/70 | 20/70 | 1/50 | 7/49 | 8/50 (16) |
| 1000 | 0/70 | 0/70 | 20/70 | 5/50 | 6/45 | 11/50 (22) |

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at weeks 52-53.
[f]Final sacrifice at weeks 104-106.

( )Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If $^{*}$, then $p < 0.05$. If $^{**}$, then $p < 0.01$.

Table 2. 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 $p < 0.01$.

References

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