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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

TXR No. 0052544

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM May 18, 2004

SUBJECT: **Epoxiconazole** REVISED Quantitative Risk Assessment (Q_1^*) Based On C57BL/6NCrlBr Mouse Dietary Study With $^3/_4$'s Interspecies Scaling Factor

P.C. Code 123909

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The revised unit risk, $Q_1^*(mg/kg/day)^{-1}$, for Epoxiconazole is 3.04×10^{-2} in human equivalents based on male mouse liver adenoma and/or carcinoma combined tumor rates. The dose levels used from the 79-week dietary study were 0, 1, 5, 200, and 500 ppm of Epoxiconazole. The corresponding tumor rates were 1/86, 0/40, 0/46, 3/48, and 34/50, respectively.

Background

On January 3, 2001, a human slope factor (Q_1^*) of 5.64×10^0 was generated based on male mouse liver adenoma and/or carcinoma combined tumor rates. This value is incorrect due to an error in one of the parameters (route of exposure) used in the calculations (TXR No. 0014429).

All unit risks have been converted from animals to humans by use of the $^3/_4$'s scaling factor (Tox_Risk program, Version 5.31, K. Crump, 2001)[1]. For the conversion to human equivalents,

[1]See memo - Deriving Q_1^*s Using the Unified Interspecies Scaling Factor, P.A. Fenner-Crisp, Director, HED, 7/1/94.

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weights of 0.03 kg for the mouse, 70 kg for humans, and the use of 79 weeks for the mouse life-span default were used.

It is to be noted that the Q_1^* $(mg/kg/day)^{-1}$ is an estimate of the upper bound on risk and that, as stated in the EPA Risk Assessment Guidelines, the true value of the risk is unknown, and may be as low as zero.

Dose-Response Analysis

The statistical evaluation of mortality (Epoxiconazole Qualitative Risk Assessment Based On Wistar Rat and C57BL/6NCrlBr Mouse Dietary Studies, L. Brunsman, 9/27/2000) indicated no significant incremental changes with increasing doses of Epoxiconazole in male or female mice. These unit risks, Q_1^*'s, were obtained by the application of the Multi-Stage model (Tox_Risk program, Version 5.31, K. Crump, 2001).

Male mice had significant increasing trends in liver adenomas, carcinomas, and adenomas and/or carcinomas combined, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 500 ppm dose group with the controls for liver adenomas at $p < 0.05$, and for carcinomas, and adenomas and/or carcinomas combined, both at $p < 0.01$.

Additional Q_1^* Calculations

The unit risk, $Q_1^*(mg/kg/day)^{-1}$, of Epoxiconazole based upon female mouse liver adenoma and/or carcinoma combined tumor rates is 1.60×10^{-2} in human equivalents. The dose levels used from the 79-week dietary study were 0, 1, 5, 200, and 1000 ppm of Epoxiconazole. The corresponding tumor rates were 1/93, 1/46, 1/48, 1/49, and 38/49, respectively.

```
Generating Model Fit Table ---
TITLE: Epoxiconazole Male Mouse Liver Combined
Model: Multistage              Dataset: C:\Program Files\TOX_RISK\epoxiconazolemmliv.txd
Functional form: 1 - EXP( -Q0 - Q1 * D - Q2 * D^2 ... - Qk * D^k )
       Chi-square: 1.0059                                P-value: 0.60
         Maximum Log-Likelihood =  -4.871009e+001
       Parameter Estimates :  k = 4
                              Q 0 = 5.830960E-003
                              Q 1 = 0.000000E+000
                              Q 2 = 0.000000E+000
                              Q 3 = 6.184505E-009
                              Q 4 = 5.768663E-012
```

Experimental Doses (ppm)	#responses/ #subjects	Expected number of responders	90.0% Binomial Limits Lower	Upper
0	1 / 86	0.50	0.034	4.629
1	0 / 40	0.23	0.000	2.888
5	0 / 46	0.27	0.000	2.901
200	3 / 48	3.00	0.825	7.354
500	34 / 50	34.00	27.802	39.357

```
Generating Statistics Table ---
Dataset: C:\Program Files\TOX_RISK\epoxiconazolemmliv.txd
TITLE: Epoxiconazole Male Mouse Liver Combined
                              Trend Test Results
       Mantel-Haenszel (Z): 1.1568E+001        P-value: less than 1E-06
                             Pearson's r:  0.705
           Comparisons against control using Fisher's Exact Test
```

Dose (ppm)	#responses/#subjects	P-value
0	1 / 86	control
1	0 / 40	1
5	0 / 46	1
200	3 / 48	0.13
500	34 / 50	less than 1E-06

```
Generating Protocol and q1* Table ---
          Dataset:  C:\Program Files\TOX_RISK\epoxiconazolemmliv.txd
                TITLE: Epoxiconazole Male Mouse Liver Combined
```

Doses (ppm)	#responses/ #subjects
0	1/86
1	0/40
5	0/46
200	3/48
500	34/50

Body Weight	0.03	kg	70	kg
LifeSpan	79	weeks	70	years
Breathing Rate	0.0347	l/min	0.833	m^3/hr
Food Consumption	3.9	g/day	1400	g/day
Drinking Rate	6	ml/day	2	l/day
Route	FOOD (ppm)		N/A	
Dosing: Hrs/Day	24		N/A	
Days/Week	7		N/A	
Weeks	79		N/A	
Weeks of Study	79		N/A	
Averaging Factor	1		1	

```
       Model: Multistage                          Risk Type: Extra Risk
Molecular Wt.:   100.000                     Confidence limit: 95.000%
           Adjustment for Experiment Length:     1.000 (EPA METHOD)
       Animal to human conversion method: MG/KG  BODY WEIGHT(3/4)/DAY
        Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
  Lower Bound = Not Reqstd    MLE = 9.8300E-006    Upper Bound = 3.0408E-002
```

```
Generating Model Fit Table ---
TITLE: Epoxiconazole Female Mouse Liver Tumors Combined
Model: Multistage              Dataset: C:\Program Files\TOX_RISK\epoxiconazolefmliv.txd
Functional form: 1 - EXP( -Q0 - Q1 * D - Q2 * D^2 ... - Qk * D^k )
       Chi-square: 0.33                                P-value: 0.85
         Maximum Log-Likelihood =  -4.634793e+001
       Parameter Estimates :  k = 4
                              Q 0 = 1.611073E-002
                              Q 1 = 1.176924E-005
                              Q 2 = 0.000000E+000
                              Q 3 = 0.000000E+000
                              Q 4 = 1.465995E-012
```

Experimental Doses (ppm)	#responses/ #subjects	Expected number of responders	90.0% Binomial Limits Lower	Upper
0	1 / 93	1.49	0.036	4.647
1	1 / 46	0.74	0.054	4.553
5	1 / 48	0.77	0.056	4.560
200	1 / 49	1.01	0.057	4.562
1000	38 / 49	38.00	32.163	42.566

```
Generating Statistics Table ---
Dataset: C:\Program Files\TOX_RISK\epoxiconazolefmliv.txd
TITLE: Epoxiconazole Female Mouse Liver Tumors Combined
                          Trend Test Results
       Mantel-Haenszel (Z): 1.3352E+001        P-value: less than 1E-06
                          Pearson's r:  0.792
            Comparisons against control using Fisher's Exact Test
```

Dose (ppm)	#responses/#subjects	P-value
0	1 / 93	control
1	1 / 46	0.55
5	1 / 48	0.57
200	1 / 49	0.57
1000	38 / 49	less than 1E-06

```
Generating Protocol and q1* Table ---
          Dataset:  C:\Program Files\TOX_RISK\epoxiconazolefmliv.txd
           TITLE: Epoxiconazole Female Mouse Liver Tumors Combined
```

Doses (ppm)	#responses/ #subjects
0	1/93
1	1/46
5	1/48
200	1/49
1000	38/49

Body Weight	0.03	kg	70	kg
LifeSpan	79	weeks	70	years
Breathing Rate	0.0347	l/min	0.833	m^3/hr
Food Consumption	3.9	g/day	1400	g/day
Drinking Rate	6	ml/day	2	l/day
Route	FOOD (ppm)		N/A	
Dosing: Hrs/Day	24		N/A	
Days/Week	7		N/A	
Weeks	79		N/A	
Weeks of Study	79		N/A	
Averaging Factor	1		1	

```
       Model: Multistage                          Risk Type: Extra Risk
Molecular Wt.:   100.000                      Confidence limit: 95.000%
          Adjustment for Experiment Length:     1.000 (EPA METHOD)
        Animal to human conversion method: MG/KG  BODY WEIGHT(3/4)/DAY
         Unit Potency [ per mg/kg/day ] (computed for Risk of 1.0E-6)
  Lower Bound = Not Reqstd    MLE = 6.2921E-004    Upper Bound = 1.5963E-002
```

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Chemical:	**1H-1,2,4-Triazole, 1-{{3-(2-chlorophenyl**
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