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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

TXR No.   0053450

<u>MEMORANDUM</u>

DATE: June 23, 2005

SUBJECT: **Pirimicarb:** Quantitative Risk Assessment (Q_1^*) Based On Alderley Park Swiss-derived Mouse Dietary Study With $^3/_4$'s Interspecies Scaling Factor

P.C. Code: 106101

TO: Guruva Reddy, Veterinary Medical Officer
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THROUGH: Jess Rowland, Branch Chief
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<u>Summary</u>

The unit risk, Q_1^* (mg/kg/day)$^{-1}$, of Pirimicarb based upon male mouse liver combined adenoma and/or carcinoma tumor rates is 3.526×10^{-2} in human equivalents. The dose levels used from the 96-week dietary study were 0, 200, 400 and 1600 ppm of Pirimicarb. The corresponding censored tumor rates for the male mouse liver combined tumors were 22/104, 18/51, 17/48 and 32/52, respectively.

<u>Background</u>

On May 11, 2005, the Carcinogenicity Assessment Review Committee recommended that a low dose extrapolation model be applied to the experimental animal tumor data and that quantifications of risk be estimated for male and female mouse liver and lung tumors for Pirimicarb. The most potent unit risk will be used for the purpose of lifetime cancer risk assessment by the

Agency. In this case, the most potent unit risk, Q_1^*, is that for male mouse liver adenoma and/or carcinoma combined tumor rates at 3.526×10^{-2} in human equivalents.

For the conversion to human equivalents, weights of 0.03 kg for the mouse, 70 kg for humans, molecular weight of 238.3, and life-span defaults of 96 weeks for male mice and 95 weeks for female mice were used. The unit risks, Q_1^*s, for male mice were obtained by MultiStage model which uses censored tumor rates. The unit risks, Q_1^*s, for female mice were obtained by the application of the time-to-tumor Weibull model, which uses uncensored tumor rates. All unit risks have been converted from animals to humans by use of the $^3/_4$'s scaling factor[1] (QRisk, STATOX for Windows program, Version 4.5, Environ International Corporation, 2005).

It is to be noted that the Q_1^* $(mg/kg/day)^{-1}$ is an estimate of the <u>upper bound</u> 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."

<u>Dose-Response Analysis</u>

A carcinogenicity study in Alderley Park Swiss-derived mice was conducted by Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, for Zeneca Ag Products, Wilmington, Delaware, and dated December 24, 1980 (Report No. CTL/P/491, MRID No. 44883803).

There were no statistically significant incremental changes in mortality with increasing doses of Pirimicarb in male mice. Female mice showed a significant increasing trend in mortality with increasing doses of Pirimicarb, as well as a significant difference in the pair-wise comparison of the 1600 ppm dose group with the controls, both at $p < 0.05$ (**Pirimicarb:** Qualitative Risk Assessment Based On Alpk:APfSD Rat, Alderley Park Swiss-derived Mouse and C57BL/10J$_f$CD-1 Alpk Mouse Dietary Studies, L. Brunsman, 4/26/2005, TXR No. 0053239).

Male mice had a significant increasing trend, and a significant difference in the pair-wise comparison of the 1600 ppm dose group with the controls, for liver adenomas and/or carcinomas combined, both at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 200 and 400 ppm dose groups with the controls for liver adenomas and/or carcinomas combined, both at $p < 0.05$.

<u>Additional Q_1^* Calculations</u>

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Pirimicarb based upon female mouse lung adenoma and/or carcinoma combined tumor rates is 3.498×10^{-2} in human equivalents. The dose levels used

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

from the 95-week dietary study were 0, 200, 400 and 1600 ppm of Pirimicarb. The uncensored tumor rates were 14/120, 9/59, 12/60 and 18/59, respectively.

The unit risk, Q_1^* (mg/kg/day)$^{-1}$ of Pirimicarb based upon female mouse liver adenoma and/or carcinoma combined tumor rates is 2.326 x 10^{-2} in human equivalents. The dose levels used from the 95-week dietary study were 0, 200, 400 and 1600 ppm of Pirimicarb. The uncensored tumor rates were 5/120, 6/57, 9/59 and 9/58, respectively.

The unit risk, Q_1^* (mg/kg/day)$^{-1}$ of Pirimicarb based upon male mouse lung adenoma and/or carcinoma combined tumor rates is 1.296 x 10^{-2} in human equivalents. The dose levels used from the 96-week dietary study were 0, 200, 400 and 1600 ppm of Pirimicarb. The censored tumor rates were 18/103, 9/51, 8/48 and 19/54, respectively.

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Risk Assessment : 669
Chemical : PIRIMICARB
Sex : male
Lesions:
     Liver : Adenoma
     Liver : Carcinoma
        Experimental   Target

	Experimental	Target
Species:	MOUSE	Human
Body Weight:	0.03000 kg	70.00 kg
Lifespan:	96 weeks	70 years
Breathing Rate:	0.34700E-01 l/min	0.83300 m^3/hr
Food Consumption:	3.90 g/day	1400.00 g/day
Drinking Rate:	6.00 ml/day	2.0 L/day
Route:	Food (ppm)	

Dosing: Hrs/Day : 24.0
    Days/Week : 7.0
    Weeks : 96.0
Weeks of Study : 96.0
Animal to Human Conversion Method: Body Weight $^\wedge$ 3/4
Adjustment for Exp. Length : EPA Method   1.0000
Conver. Factor 1 (from route units to mg/kg/day)   0.13000
Conver. Factor 2 (from mg/kg/day to a-to-h units)   0.41618
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.34572

Overall Conversion Factor = 1.87046E-02
  Model: Multistage
    $p(d) = 1 - \exp(-q0 - q1 * d - q2 * d^\wedge 2 - q3 * d^\wedge 3)$
        Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (ppm)	Human Equivalent per (mg/kg/day)
q(0) =	0.260604740756	0.260604740756
q(1) =	4.56021759471E-04	2.438015089682E-02
q(2) =	0.00000000000	0.00000000000
q(3) =	0.00000000000	0.00000000000

    Maximum Log-likelihood -153.112236769

Group	Untransformed Dose (ppm)	Human Dose (mg/kg/day)	#Responses Observed/#Animals	#Responses Predicted	90% Binomial Limits Lower	Upper
1	0.00000	0.00000	22/ 104	23.86	15.41	30.00
2	200.000	3.74093	18/ 51	15.13	12.39	24.30
3	400.000	7.48185	17/ 48	17.18	11.55	23.13
4	1600.00	29.9274	32/ 52	32.68	25.62	37.84

    Chi-Square Statistic = 1.0057   d.f. = 2 p_value = 0.60481
      Calculations are based on Extra Risk
      Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)
Lower Bound = 1.38404E-03 MLE= 2.43801E-02 Upper Bound (q1*)= 3.52626E-02

Extra Risk	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10000	2.9879	4.3216	13.276
5.00000E-02	1.4546	2.1039	8.4924
1.00000E-02	0.28501	0.41223	2.9371
5.00000E-03	0.14215	0.20560	1.8674
1.00000E-03	2.83728E-02	4.10375E-02	0.56295
1.00000E-04	2.83600E-03	4.10190E-03	6.98146E-02
1.00000E-05	2.83588E-04	4.10172E-04	7.20165E-03
1.00000E-06	2.83586E-05	4.10170E-05	7.22523E-04

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Risk Assessment : 670
Chemical : PIRIMICARB
Sex : female
Lesions:
    Lung : Adenoma
    Lung : Carcinoma
        Experimental   Target

	Experimental	Target
Species:	MOUSE	Human
Body Weight:	0.03000 kg	70.00 kg
Lifespan:	95 weeks	70 years
Breathing Rate:	0.34700E-01 l/min	0.83300 m^3/hr
Food Consumption:	3.90 g/day	1400.00 g/day
Drinking Rate:	6.00 ml/day	2.0 L/day

Route: Food (ppm)
Dosing: Hrs/Day : 24.0
    Days/Week : 7.0
    Weeks : 95.0
Weeks of Study : 95.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Conver. Factor 1 (from route units to mg/kg/day) 0.13000
Conver. Factor 2 (from mg/kg/day to a-to-h units) 0.41618
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.34572

Overall Conversion Factor = 1.87046E-02
  Model: Time-to-Tumor Weibull

$$p(d) = 1 - \exp((-q0 - q1 * d - q2 * d^2 - q3 * d^3) * (t - t0)^c)$$

    Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (ppm)	Human Equivalent per (mg/kg/day)
q(0) =	3.714306832075E-06	7.722940330967E-06
q(1) =	5.422730570125E-09	6.028007063832E-07
q(2) =	1.349930811689E-12	8.022653938787E-09
q(3) =	0.00000000000	0.00000000000
c =	2.39701072405	2.39701072405
t0 =	0.00000000000 (weeks)	0.00000000000 (years)

    Maximum Log-likelihood -123.896618081

Group	Untransformed Dose (ppm)	Human Dose (mg/kg/day)	#Incidental Responses Observed	#Fatal Responses Observed	#Animals
1	0.00000	0.00000	14	0	120
2	200.000	3.74093	9	0	59
3	400.000	7.48185	12	0	60
4	1600.00	29.9274	18	0	59

    Calculations are based on Extra Risk
Risk calculations at time 95.0 wks (animal) equiv. to 70 yrs (Human)
    Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)
Lower Bound = 2.42645E-06 MLE= 1.59549E-02 Upper Bound (q1*)= 3.49821E-02

Extra Risk	Time (yrs)	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10	70	3.0536	6.1073	19.465
0.05	70	1.4663	3.0880	15.313
0.01	70	0.28730	0.62473	8.8938
0.005	70	0.14329	0.31287	7.0531
0.001	70	2.86004E-02	6.26559E-02	4.1219
0.0001	70	2.85875E-03	6.26747E-03	1.9129
1.000E-5	70	2.85862E-04	6.26765E-04	0.88790
1.000E-6	70	2.85861E-05	6.26767E-05	0.41213

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Risk Assessment : 670
Chemical : PIRIMICARB
Sex : female
Lesions:
     Liver : Adenoma
     Liver : Carcinoma
         Experimental   Target

	Experimental	Target
Species:	MOUSE	Human
Body Weight:	0.03000 kg	70.00 kg
Lifespan:	95 weeks	70 years
Breathing Rate:	0.34700E-01 l/min	0.83300 m^3/hr
Food Consumption:	3.90 g/day	1400.00 g/day
Drinking Rate:	6.00 ml/day	2.0 L/day

Route: Food (ppm)
Dosing: Hrs/Day : 24.0
    Days/Week : 7.0
    Weeks : 95.0
Weeks of Study : 95.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Conver. Factor 1 (from route units to mg/kg/day) 0.13000
Conver. Factor 2 (from mg/kg/day to a-to-h units) 0.41618
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.34572

Overall Conversion Factor = 1.87046E-02
  Model: Time-to-Tumor Weibull
    $p(d) = 1 - \exp((-q0 - q1 * d - q2 * d^2 - q3 * d^3) * (t - t0)^c)$
    Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (ppm)	Human Equivalent per (mg/kg/day)
q(0) =	2.046698420864E-06	4.190557257767E-06
q(1) =	5.357272265101E-09	5.864249863331E-07
q(2) =	0.00000000000	0.00000000000
q(3) =	0.00000000000	0.00000000000
c =	2.34659074890	2.34659074890
t0 =	0.00000000000 (weeks)	0.00000000000 (years)

    Maximum Log-likelihood -86.1594866141

Group	Untransformed Dose (ppm)	Human Dose (mg/kg/day)	#Incidental Responses Observed	#Fatal Responses Observed	#Animals
1	0.00000	0.00000	5	0	120
2	200.000	3.74093	6	0	57
3	400.000	7.48185	9	0	59
4	1600.00	29.9274	9	0	58

    Calculations are based on Extra Risk
Risk calculations at time 95.0 wks (animal) equiv. to 70 yrs (Human)
    Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)
Lower Bound = 1.32814E-03 MLE= 1.25286E-02 Upper Bound (q1*)= 2.32566E-02

Extra Risk	Time (yrs)	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10	70	4.5304	8.4096	22.272
0.05	70	2.2055	4.0941	13.649
0.01	70	0.43215	0.80219	4.2112
0.005	70	0.21553	0.40009	2.5394
0.001	70	4.30201E-02	7.98573E-02	0.67060
0.0001	70	4.30007E-03	7.98214E-03	7.49600E-02
1.000E-5	70	4.29988E-04	7.98178E-04	7.58412E-03
1.000E-6	70	4.29986E-05	7.98174E-05	7.52933E-04

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date: 06/23/2005 at time: 11:02

Risk Assessment : 669
Chemical : PIRIMICARB
Sex : male
Lesions:
        Lung : Adenoma
        Lung : Carcinoma
                Experimental   Target

Species:	MOUSE	Human
Body Weight:	0.03000 kg	70.00 kg
Lifespan:	96 weeks	70 years
Breathing Rate:	0.34700E-01 l/min	0.83300 m^3/hr
Food Consumption:	3.90 g/day	1400.00 g/day
Drinking Rate:	6.00 ml/day	2.0 L/day

Route: Food (ppm)
Dosing: Hrs/Day : 24.0
        Days/Week : 7.0
        Weeks : 96.0
Weeks of Study : 96.0
Animal to Human Conversion Method: Body Weight ^ 3/4
Adjustment for Exp. Length : EPA Method   1.0000
Conver. Factor 1 (from route units to mg/kg/day)   0.13000
Conver. Factor 2 (from mg/kg/day to a-to-h units)   0.41618
Conver. Factor 3 (from a-to-h units to target mg/kg/day) 0.34572

Overall Conversion Factor = 1.87046E-02
  Model: Multistage
    $p(d) = 1 - \exp(-q0 - q1 * d - q2 * d^2 - q3 * d^3)$
        Maximum Likelihood Estimates of Dose Coefficients

	Untransformed per (ppm)	Human Equivalent per (mg/kg/day)
q(0) =	0.189330222403	0.189330222403
q(1) =	0.00000000000	0.00000000000
q(2) =	0.00000000000	0.00000000000
q(3) =	5.955612145681E-11	9.100785472095E-06

        Maximum Log-likelihood -128.159214446

Group	Untransformed Dose (ppm)	Human Dose (mg/kg/day)	#Responses Observed/#Animals	#Responses Predicted	90% Binomial Limits Lower	Upper
1	0.00000	0.00000	18/ 103	17.77	11.99	25.59
2	200.000	3.74093	9/ 51	8.82	4.83	14.66
3	400.000	7.48185	8/ 48	8.43	4.07	13.45
4	1600.00	29.9274	19/ 54	18.99	13.23	25.47

        Chi-Square Statistic = 0.34993E-01 d.f. = 2 p_value = 0.98266
        Calculations are based on Extra Risk
        Unit potency (per mg/kg/day) (Computed for Risk of 1.E-6)
Lower Bound = 1.48358E-06 MLE= 2.08782E-06 Upper Bound (q1*)= 1.29640E-02

Extra Risk	95.0% Lower Bound on Dose (mg/kg/day)	MLE Doses (mg/kg/day)	95.0% Upper Bound on Dose (mg/kg/day)
0.10000	8.1271	22.622	32.519
5.00000E-02	3.9566	17.796	25.044
1.00000E-02	0.77525	10.336	14.546
5.00000E-03	0.38665	8.1971	11.536
1.00000E-03	7.71751E-02	4.7905	6.7416
1.00000E-04	7.71404E-03	2.2232	3.1287
1.00000E-05	7.71369E-04	1.0319	1.4522
1.00000E-06	7.71365E-05	0.47897	0.67404