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

MEMORANDUM

December 8, 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Difenoconazole (DIVIDEND™) Quantitative Risk Assessment (Q_1^*) Based On Charles River CD-1 Mouse Chronic Dietary Study With $^3/_4$'s Interspecies Scaling Factor

P.C. Code 128847

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Summary

The upper bound estimate of unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Difenoconazole (DIVIDEND™) based upon male mouse liver adenoma and/or carcinoma combined tumor rates is 1.57×10^{-1} in human equivalents. The dose levels used in this assessment were 0, 1.51, 4.65, and 46.29 mg/kg/day. The corresponding tumor rates were 5/68, 10/57, 9/58, and 9/56, respectively.

This Q_1^* has been converted from animals to humans by use of the $^3/_4$'s scaling factor and obtained by the application of the time-to-tumor Weibull model (Tox_Risk program, Version 3.5, K. Crump, 1994)[1].

Background

On May 18, 1994, the Carcinogenicity Peer Review Committee concluded that "for the purpose of risk characterization the Margin of Exposure (MOE) approach should be used for quantification of human risk" and that "the mouse study may not have been an appropriate test, due to the excessive toxicity in both

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

sexes at the two top doses (2500 and 4500 ppm)" (Carcinogenicity Peer Review of Difenoconazole (DIVIDEND™), J. Rowland and E. Rinde, 7/27/94). The Risk Assessment Review Committee has since requested that a Q_1^* be generated. The male mouse liver adenoma and/or carcinoma combined tumors were chosen because this results in the most conservative Q_1^* when the top two doses are excluded from the analysis.

The statistical evaluation (Dividend (Difenoconazole) Qualitative Risk Assessment Based On Charles River CD-1 Mouse Dietary Study, L. Brunsman, 3/30/94) indicated a significant increasing trend in mortality with increasing doses of Difenoconazole (DIVIDEND™) in male mice. The male mice had a significant dose-related increasing trend at $p < 0.01$, and a significant difference in the pair-wise comparison of the 423.16 mg/kg/day dose group with the controls at $p < 0.05$ and in the pair-wise comparison of the 818.87 mg/kg/day dose group with the controls at $p < 0.01$, for liver adenomas and/or carcinomas combined. Because the carcinogenicity peer review committee considered both the 423.16 and 818.87 mg/kg/day dose groups to be excessive, these dose groups have been excluded from the calculation of the Q_1^*.

For the conversion to human equivalents, weights of 0.03 kg for the mouse, 70 kg for humans and the $^3/_4$'s scaling factor 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."

RA# 312; 312; 312; Male

Dataset: C:\TOXVER35\DIFENOCO.TXS\MMLIVCOM

Exposure Pattern

Model: Multistage Weib Age Begins: 0 Age Ends: 70

Target Species: Human Weeks/Year: 52 Days/Week: 7

Route: Food 100 % Hours/Day : 24

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)

MLE = 2.8046E-002 Upper Bound(q1*) = 1.5695E-001

Dose Estimates (ppb)

Fatal Extra Risk	Time	95.000% Lower Bound	MLE
1.0000E-006	70.00	3.1858E-001	1.7828E+000
1.0000E-005	70.00	3.1858E+000	1.7828E+001
0.0001	70.00	3.1859E+001	1.7829E+002
0.0010	70.00	3.1874E+002	1.7837E+003
0.01	70.00	3.2018E+003	1.7918E+004
0.10	70.00	3.3566E+004	1.8784E+005