7-19-94

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: Iprodione, Quantitative Risk Assessment, Two-Year Rat (Charles River Sprague-Dawley, MRID Nos. 416353-01 & 416353-02) Dietary Study

Caswell no.470A

From: Bernice Fisher, Biostatistician
Statistics Section
Science Analysis Branch
Health Effects Division (7509C)

Bernice Fisher 7/19/94

To: Linda Taylor, Ph.D., Pharmacologist
Review Section II
Toxicology Branch II
Health Effects Division (7509C)

Thru: Hugh Pettigrew, Ph.D., Section Head
Statistics Section
Science Analysis Branch
Health Effects Division (7509C)

Hugh M. Pettigrew 7/19/94

Summary

The unit risk, $Q_1^*(mg/kg/day)^{-1}$, of Iprodione, based upon rat interstitial cell benign tumor rates in the testes is $4.39x10^{-2}$ $(mg/kg/day)^{-1}$ in human equivalents[a]. The dose levels used in the rat study were 0, 150, 300, and 1600 ppm. of Iprodione. The corresponding tumor rates were 3/51, 7/57, 7/52 and 29/59 respectively.

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Iprodione, based upon liver (adenomas &/or carcinomas) tumor rates in mice, for males is $8.70x10^{-3}$ $(mg/kg/day)^{-1}$ and for the females is $5.07x10^{-3}$ $(mg/kg/day)^{-1}$, both in human equivalents[a]. The dose levels used from the mouse study were 0, 160, 800, and 4000 ppm. of Iprodione. The corresponding tumor rates for males were 7/62, 6/62, 11/62, 27/63 respectively, and for females were 2/47, 2,49, 2/49 21/48 respectively.

[a] The 3/4's interspecies scaling factor was used to determine human equivalence of the unit risk derived from the animal study.

Background

In February, 1994 the Peer Review Committee recommended that a quantitative risk assessment for Iprodione be estimated from rat interstitial cell tumors of the testes, and also from the mouse male and female liver (adenomas and/or carcinomas) tumors separately.

The statistical evaluation (Iprodione-Qualitative Risk Assessment-Based on Charles River Sprague-Dawley Rat and CD-1 Mouse Dietary Studies, L.Brunsman 1/94) indicated that there was a significant decreasing trend in mortality with dose increments of Iprodione in rats and no significant dose related changes in the mice.

Male rats had significantly increasing trends in interstitial cell (benign) tumor rates with dose increments of Iprodione, and also significant differences in the pair-wise comparison of the 1600 ppm dose level and the controls.

Both male and female mice had significant dose related increasing trends and significant differences in the pair-wise comparisons of the 4000 ppm dose level and the controls in liver (adenomas and/or carcinomas) tumor rates.

Dose-Response

Estimates of risk, Q^{1*}, were caculated for the rat benign testicular tumor rates and the male and female liver tumor rates separately.

Since male rats had significant differential mortality with incremental doses of Iprodione, the estimates of the unit risk, Q_1^*, were obtained by the application of the Multi-Stage Weib model (Tox_Risk program, version 3.5- K.Crump).

Since neither male or female mice had significant mortality changes with incremental doses of Iprodione, the estimates of unit risk, Q_1^*, were obtained by the application of the Linearized Multi-Stage model (Tox_Risk program, version 3.5- K.Crump).

The resulting estimates of unit risk, Q_1^*, are as follows:

Species: Strain	Tumor	Q_1^* $(mg/kg/day)^{-1}$ in Human Equivalents
Rat: Sprague-Dawley	Interstitial cell tumors of testes	4.39×10^{-2}
Mouse: CD-1	Liver (Ad &/or Ca) tumors	
Males		8.70×10^{-3}
Females		5.07×10^{-3}

Additional Estimates of Q_1^* for Iprodione

The above estimates of unit risk, Q_1^*, were obtained using the interspecies scaling factor, i.e. using human-animal body weights to the 3/4's power, to give human equivalents of the results from either rat or mouse data, as now determined by HED policy (Deriving Q*s Using the Unified Interspecies Scaling Factor, P.A. Fenner-Crisp, Director, HED -7/1/94).

The following estimates of unit risk, Q_1^*, were obtained from using surface area adjustments, human-animal body weights to the 2/3's power to give the human equivalents of either rat or mouse data, as previosly used by HED.

The results are as follows:

Species:Strain	Tumor	Q_1^* $(mg/kg/day)^{-1}$ in Human Equivalents
Rat: Sprague-Dawley	Interstitial cell tumors of testes	6.82×10^{-2}
Mouse: CD-1	Liver (Ad &/or CA) tumors	
Males		1.66×10^{-2}
Females		9.68×10^{-3}

It is to be noted that 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."