Attachment 7

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

014020

MEMORANDUM

March 2, 2000

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: REVISED CGA 184927 (Clodinafop-Propargyl) Quantitative Risk Assessment (Q_1^*) Based On Tif:RAIf(SPF) Albino Rat and Tif:MAGf(SPF) Albino Mouse Chronic Dietary Studies With $^3/_4$'s Interspecies Scaling Factor

TO: Yung Yang, Toxicologist
Toxicology Branch 1
Health Effects Division (7509C)

FROM: Lori L. Brunsman, Statistician
Science Analysis Branch
Health Effects Division (7509C)

Lori L. Brunsman

THROUGH: William L. Burnam, Branch Chief
Science Analysis Branch
Health Effects Division (7509C)

The most potent unit risk, $Q_1^*(mg/kg/day)^{-1}$, of those calculated for CGA 184927 (Clodinafop-Propargyl) is that for male mouse liver benign hepatoma and/or carcinoma combined tumor rates at 1.29×10^{-1} in human equivalents. The dose levels used from the 78-week dietary study were 0, 1, 10, 100, and 250 ppm of CGA 184927. The corresponding tumor rates were 9/58, 13/57, 9/57, 14/57, and 38/57, respectively.

Background

On September 29, 1999, the Cancer Assessment Review Committee met to classify the carcinogenic potential of CGA 184927 (Clodinafop-Propargyl). Quantifications of risk have subsequently been estimated. The most potent unit risk will be used for further calculations by the Agency. In this case, the most potent unit risk, Q_1^*, is that for male mouse liver benign hepatoma and/or carcinoma combined tumor rates at 1.29×10^{-1} in human equivalents.

All unit risks have been converted from animals to humans by use of the $^3/_4$'s scaling factor (Tox_Risk program, Version 3.5, K. Crump, 1994)[1]. For the conversion to human equivalents, weights of 0.03 kg for the mouse, 0.35 kg for the rat, 70 kg for humans, and

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

the use of 78 weeks for the mouse life-span default and 105 weeks for the rat 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 (CGA 184927™ Qualitative Risk Assessment Based On Tif:RAIf(SPF) Albino Rat and Tif:MAGf(SPF) Albino Mouse Dietary Studies, L. Brunsman, 8/4/99) indicated significant increasing trends for mortality with increasing doses of CGA 184927 in male mice. The unit risk, Q_1^*, for male mice was obtained by the application of the time-to-tumor Weibull model (Tox_Risk program, Version 3.5, K. Crump, 1994). There were no significant incremental changes in mortality with increasing doses of CGA 184927 in male or female rats. The unit risks, Q_1^*'s, for male and female rats were obtained by the application of the Multi-Stage model (Tox_Risk program, Version 3.5, K. Crump, 1994).

Male mice had a significant increasing trend, and a significant difference in the pair-wise comparison of the 250 ppm dose group with the controls, for hepatocellular benign hepatomas and/or carcinomas combined, both at $p < 0.01$.

Male rats had a significant increasing trend, and a significant difference in the pair-wise comparison of the 750 ppm dose group with the controls, for prostate adenomas and/or carcinomas combined, both at $p < 0.01$.

Female rats had a significant increasing trend at $p < 0.01$, and a significant difference in the pair-wise comparison of the 750 ppm dose group with the controls at $p < 0.05$, for ovarian tubular adenomas.

Additional Q_1^* Calculations

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of CGA 184927 based upon male rat prostate adenoma and/or carcinoma combined tumor rates is 3.16×10^{-2} in human equivalents. The dose levels used from the 105-week dietary study were 0, 1, 10, 300, and 750 ppm of CGA 184927. The corresponding tumor rates were 8/67, 9/68, 12/67, 12/68, and 20/67, respectively.

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of CGA 184927 based upon female rat ovarian tubular adenoma tumor rates is 9.25×10^{-3} in human equivalents. The dose levels used from the 106-week dietary study were 0, 1, 10, 300, and 750 ppm of CGA 184927. The corresponding tumor rates were 2/67, 1/65, 1/70, 1/68, and 9/66, respectively.

2