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MEMORANDUM July 7, 1999

SUBJECT: Atrazine™ Quantitative Risk Assessment (Q_1^*) Based On Sprague-Dawley Female Rat Chronic Dietary Studies Using mg/kg b.w.$^{3}/_{4}$'s/day Cross-Species Scaling Factor

P.C. Code 080803

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The most potent unit risk, $Q_1^*(mg/kg/day)^{-1}$, of those calculated for Atrazine is that for the Morseth study (1998) female rat mammary gland adenoma and/or carcinoma combined tumor rates at 1.12×10^{-1} in human equivalents. The dose levels used from the 105-week dietary study were 0, 25, 50, 70, and 400 ppm. The corresponding tumor rates were 12/80, 18/80, 21/79, 14/80, and 27/80, respectively.

Background

On September 10, 1987, the Carcinogenicity Peer Review Committee classified Atrazine as a category C carcinogen (possible human carcinogen) and recommended that a quantitative risk assessment be estimated for mammary gland tumors in female rats (Peer Review of Atrazine, J.W. Hauswirth, 3/1/88). A quantitative risk assessment (ATRAZINE - Updated Qualitative and Quantitative Risk Assessment from a Rat 2-Year Chronic Oral Toxicity/Oncogenicity Study, C.J. Nelson, 8/23/88) was prepared using the $^{2}/_{3}$'s scaling factor. This revised quantitative risk assessment reflects the Division change from use of

the $^{2}/_{3}$'s to the $^{3}/_{4}$'s scaling factor in 1994[1].

Considering both chronic rat studies submitted to the agency to date, the most potent unit risk, Q_1^*, will be used for further calculations by the Agency. In this case, the most potent unit risk, Q_1^*, is that for the Morseth study (1998) female rat mammary gland adenoma and/or carcinoma combined tumor rates at 1.12×10^{-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 0.35 kg for the rat and 70 kg for humans 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 (ATRAZINE - Updated Qualitative and Quantitative Risk Assessment from a Rat 2-Year Chronic Oral Toxicity/Oncogenicity Study, C.J. Nelson, 8/23/88, and Atrazine Qualitative Risk Assessment Based On Female Sprague-Dawley Rat Dietary Study, L. Brunsman, 2/9/99) indicated significant increasing trends with increasing doses of Atrazine in female rats of both the Mayhew (1986) and Morseth (1998) studies. Therefore, the estimates of unit risk, Q_1^*, for female rats were obtained by the application of the time-to-tumor Weibull model (Tox_Risk program, Version 3.5, K. Crump, 1994).

Female rats of the Morseth study (1998) had significant increasing trends, and significant differences in the pair-wise comparisons of the 400 ppm dose group with the controls, for mammary gland carcinomas and adenomas and/or carcinomas combined, all at $p < 0.01$. There was also a significant pair-wise comparison of the 50 ppm dose group with the controls for mammary gland adenomas and/or carcinomas combined at $p < 0.05$.

Female rats of the Mayhew study (1986) had significant increasing trends, and significant differences in the pair-wise comparisons of the 1000 ppm dose group with the controls, for mammary gland adenocarcinomas, adenomas and/or adenocarcinomas combined and adenomas and/or adenocarcinomas and/or carcinosarcomas combined, all at $p <$

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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.

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0.01. There were also significant pair-wise comparisons of the 70 and 500 ppm dose groups with the controls for mammary gland adenocarcinomas, adenomas and/or adenocarcinomas combined and adenomas and/or adenocarcinomas and/or carcinosarcomas combined, all at $p < 0.05$. When the 1000 ppm dose group is excluded from the analyses, female rats of the Mayhew study (1986) had significant increasing trends, and significant differences in the pair-wise comparisons of the 70 and 500 ppm dose groups with the controls, for mammary gland adenocarcinomas, and adenomas and/or adenocarcinomas combined, all at $p < 0.05$.

Additional Q_1^* Calculations

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Atrazine based upon the Mayhew study (1986) female rat mammary gland adenoma and/or adenocarcinoma combined tumor rates is 6.44×10^{-2} in human equivalents. The dose levels used from the 106-week dietary study were 0, 10, 70, 500, and 1000 ppm. The corresponding tumor rates were 16/87, 16/67, 27/69, 27/68, and 45/88, respectively.

The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Atrazine based upon the Mayhew study (1986) female rat mammary gland adenoma and/or adenocarcinoma and/or carcinosarcoma combined tumor rates is 6.83×10^{-2} in human equivalents. The dose levels used from the 106-week dietary study were 0, 10, 70, 500, and 1000 ppm. The corresponding tumor rates were 16/87, 16/67, 27/69, 27/68, and 47/88, respectively.

When the 1000 ppm dose group is excluded from the analyses, the unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Atrazine based upon the Mayhew study (1986) female rat mammary gland adenoma and/or adenocarcinoma combined tumor rates is 8.05×10^{-2} in human equivalents. The dose levels used from the 106-week dietary study were 0, 10, 70, and 500 ppm. The corresponding tumor rates were 16/87, 16/67, 27/69, and 27/68, respectively.