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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Simazine - Quantitative Risk Assessment, Two Year Chronic/Oncogennicity Sprague-Dawley Rat Study

caswell no. 740

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Summary

The unit risk, Q_1^*, of simazine is 1.20×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents. This estimate of Q_1^* is based upon mammary gland carcinomas in female Sprague-Dawley rats with dose levels of 0, 10, 100, and 1000 ppm.

Female rats had a significantly increasing trend in mortality with dose increments of simazine. There were significant differences in mortality in 2 dose groups, 100 and 1000 ppm as compared with controls. The females exhibited a significantly increasing trend in mammary gland carcinomas with increasing doses of simazine. In the pairwise comparison with controls, 2 dose levels, 100 and 1000 ppm, were also significantly different. See the memorandum on "Simazine - Qualitative Risk Assessment from a Rat Two Year Oral Chronic Toxicity and Oncogenicity Study, Dynamac (Dynamac no. 1-16, EPA: 68-D8-0565) - 10/18/88 for details.

Background

The Peer Review Committee on simazine on 5/17/89 concluded that the chemical compound should be classified as a [C_g] carcinogen. In addition they recommended that the unit risk, Q_1^*, should be estimated from the female rat mammary gland carcinoma tumor rates.

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Dose-Response Analysis

As a result of the Peer Review Committee's recommendation of the use of rat mammary gland carcinomas for the estimation of Q_1^* and since there was a significantly increasing trend in mortality in female rats with dose increments of simazine, the calculation of the unit risk was made by the use of Weibull83 (time-to-death with tumor multistage model by K.Crump) computer program. The unit risk calculated from the female data in ppm doses was converted to rat mg/kg/day by the use of Lehman's Tables and then to human equivalents by the use interspecies surface area adjustments as recommended by EPA Cancer Guidelines (1986).

The resultant estimate of Q_1^* is as follows:

	Rat, Q_1^* $(mg/kg/day)^{-1}$	In Human Equivalents
female mammary gland carcinoma tumors	2.25×10^{-2}	1.20×10^{-1}

It is to be noted that Q_1^* is an estimate of the upper (95%) bound on risk and that (as stated in the EPA Guidelines) the "true value of the risk is unknown and that the lower limit of the risk may be as low as zero".

References:

Krewski, D., Crump, K.S., Farmer, J., Gaylor, D.W., Howe, R., Portier, C., Salsburg, D., Sielken, R.L., Van Ryzin, J. (1983) A Comparison of Statistical Methods for Low Dose Extrapolation Utilizing Time-to-Tumor Data. Fundamental and Applied Toxicology 3: 140-160.