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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

May 26, 1983

TO: William Burnam, Acting Chief
Toxicology Branch, HED (TS-769)

SUBJECT: Low-Dose Risk Extrapolation of thyroid, C-Cell, findings in 2-year feeding study of glyphosate in female Sprague-Dawley (C/D) rats reported by Charles C. Capen.

Dr. Capen found 6/47, 3/49, 8/50, 8/47 animals with Adenoma and/or carcinoma in the C-Cells of the thyroid. Testing this distriution for homogeneity reveals a chi square of 8.893 with 3 degrees of freedom so that the one-sided P=.015, a statistically significant value indicating the response of the groups is not similar. When the rates are weighted by the glyphosate doses of 0, 3, 10 and 30 (mg/kg/d) respectively, the Armitage test for trend partitions the overall chi-square value yielding a linear trend component of 2.805 and the departure from linearity component of 6.087. The departure from linearity accounts for 2 degrees of freedom so that the non linearity of the data i.e., the low response rate at 3 ppm is statistically significant at P <.05. No pairwise comparison yields a P value smaller than .05. We therefore conclude that the data are not statistically significant at any level which might be of regulatory concern. Moreover, Dr. Capen found C-Cell Carcinomas in 1/47 controls; 0/49 fed 3 mg/kg/d; 1/50 fed 10 mg/kg/d and 5/47 fed 30 mg/kg/d. The Fisher's Exact Test of 1/47 vs 5/47 has a P value of 0.1017, at most a borderline finding. Tests of trend on these data are not scientifically feasible because the effect of the dose level is greater than the rate of occurrence so that the effect computed would reflect the differences in glyphosate dose level rather than the rate of carcinoma incidence. Ordinarily this would not be sufficient basis for a risk assessment to be considered.

Nevertheless low-dose extrapolation has been performed for the carcinoma data by the one-hit, multi-stage, multi-hit and Mantel-Bryan Models following your request. The data will not compute using the Krewski program for Logit, Probit or Weibull models. The difficulty is that only one response level exceeds the control rate.

When the surface area correction is applied the human equivalents of the dose levels become 0, 0.15, 0.5 and 1.50 mg/kg/d. In the table below we show virtually safe dose levels, i.e., lower 95% confidence bounds for the dose associated with risks of 1×10^{-2} to 1×10^{-8} of cancer in humans. If this surface are correction is not used these Virtually Safe Dose Levels (VSD) could be increased 5-fold.

Attributable Risk Level	95% Lower Confidence Bound on VSD (mg/kg/d)			
	Mantel-Bryan	One-Hit	Multi-Hit	Multi-Stage
1×10^{-2}		6.34×10^{-2}	2.08×10^{-2}	9.66×10^{-2}
1×10^{-3}	2.17×10^{-2}	6.31×10^{-3}	2.07×10^{-4}	9.61×10^{-3}
1×10^{-4}	5.10×10^{-3}	6.31×10^{-4}	1.97×10^{-6}	9.61×10^{-4}
1×10^{-3}	1.45×10^{-3}	6.31×10^{-5}	1.86×10^{-8}	9.61×10^{-5}
1×10^{-6}	4.71×10^{-4}	6.31×10^{-6}	1.75×10^{-10}	9.61×10^{-6}
1×10^{-7}	1.69×10^{-4}	6.31×10^{-7}	1.64×10^{-12}	9.61×10^{-7}
1×10^{-8}	6.52×10^{-5}	6.31×10^{-8}	1.53×10^{-14}	9.61×10^{-8}

Note that one-hit and multi-stage model differ only due to computational procedures. The $Q_1^* = .104$ for the multi-stage model (again omitting the surface area correction would permit division by 5.)

The total TMRC represents an exposure of .024 mg/kg/d and this is associated with an upper 95% limit of risk of 2.5×10^{-3}. Of this figure potable water accounts for .017 mg/kg/day for a upper 95% C Bound on Risk of 1.7×10^{-3}. Without the surface area corrections, the risk from the TMRC and water use would be 5×10^{-4} and 3.4×10^{-4}, respectively.

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