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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: P-Chloroaniline (Dimilin Metabolite)-Quantitative Risk, Q_1^*, (Updated) from NTP Rat Oncogenicity Study

Caswell No. 182

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Summary

The revised estimated unit risk, $Q_1^*(mg/kg/day)^{-1}$ of P-Chloroaniline, based upon spleen sarcoma rates in male rats is $6.38x10^{-2}$ in human equivalents (converted from animals to humans by use of the 3/4's scaling factor-1994,Tox_Risk,3.5-K.Crump)[a]. The dose levels used in the rat gavage study were 0, 2, 6, and 18 mg/kg/day of P-Chloroaniline (Dimilin metabolite). The corresponding tumor rates in male rats were 0/46, 1/50, 3/48, and 38/50.

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

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The estimated unit risk, Q_1^*, of P-Chloroaniline was derived separately from male rat hemangiosarcomas, osteosarcomas, and fibrosarcomas and for the combination of all three sarcomas of the spleen. The results are as follows:

Hemangiosarcoma	1.39×10^{-2}
Osteosarcoma	2.59×10^{-2}
Fibrosarcoma	6.44×10^{-2}
All 3 Sarcomas	6.38×10^{-2}

Background

NTP evaluated a two-year oncogenicity study in F344/N rats. The 50 animals in each group were fed by gavage in H_2O of 0, 2, 6 and 18 mg/kg of P-Chloroaniline, a metabolite of Dimilin for 5 days per week for 103 weeks. The following tables present the summarized data and the statistical results as prepared by L.Brunsman (P-Chloroanaline Qualitative Risk Assessment Based on Charles River Fischer 344/N Rat Oral Gavage Study, 11/94) 11/94.

Male Rat spleen sarcoma tumor rates, (%), and p values:

Hemangiosarcoma	0/46	0/50	0/48	4[a]/50
(%)	(0)	(0)	(0)	(8)
p=	0.004**	1.000	1.000	0.069
Osteosarcoma	0/46	0/50	1/48	19[b]/50
(%)	(0)	(0)	(2)	(38)
p=	0.000**	1.000	0.511	0.000**
Fibrosarcoma	0/46	1/50	2/48	17[c]/50
(%)	(0)	(2)	(4)	(34)
p=	0.000**	0.521	0.258	0.000**
Total male rats with Sarcomas	0/46	1/50	3/48	38[d]/50
(%)	(0)	(2)	(6)	(76)
p=	0.000**	0.521	0.129	0.000**

[a] First hemagiosarcoma observed at week 89, dose 18 mg/kg/day
[b] First osteosarcoma observed at week 71, dose 18 mg/kg/day
[c] First fibrosarcoma observed at week 75, dose 18 mg/kg/day
[d] Two animals in the 18 mg/kg/day dose group had both a hemangiosarcoma and a fibrosarcoma.

Dose-Response Analysis

Even though there was statistical evidence of differential survival in dose levels for male rats, the estimate of unit risk, Q_1^*, was calculated from the general Linearized Multi-Stage model of K.Crump, Toxi-risk program, version 3.5 because of lack of adequate time-adjusted tumor data in all dose levels except the highest one.

The resulting estimates of unit risk, Q_1^*, were converted to human equivalents, by the use of weights of .400 kg for the rats and 70 kg for humans and the 3/4's scaling factor for interspecies extrapolation.

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."