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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: P-Chloroaniline Qualitative Risk Assessment Based On
Charles River Fischer 344/N Rat Oral Gavage Study

Caswell No. 182

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Summary

This qualitative risk assessment of p-Chloroaniline was based upon a chronic toxicology and carcinogenesis study conducted in Charles River Fischer 344/N rats. The animals received oral gavage dose levels of 0, 2, 6, or 18 mg/kg/day of p-Chloroaniline in aqueous hydrochloric acid for 103 weeks.

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of p-Chloroaniline in male or female rats.

Male rats had significant dose-related increasing trends in spleen fibrosarcomas, hemangiosarcomas, osteosarcomas and combined sarcomas. There were significant differences in the pair-wise comparisons of the 18 mg/kg/day dose group with the controls for spleen fibrosarcomas, osteosarcomas and combined sarcomas.

Female rats had no significant dose-related increasing trends and no significant differences in the pair-wise comparisons of the dosed groups with the controls for tumors of the spleen.



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Background

A chronic toxicology and carcinogenesis oral gavage study in Charles River Fischer 344/N rats was conducted by Battelle Columbus Laboratories, Columbus, Ohio, for the National Toxicology Program, Research Triangle Park, North Carolina, for the U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, and issued in July, 1989 (NTP Technical Report No. 351; NIH Pub. No. 89-2806).

The study design allocated groups of 49 or 50 rats per sex to dose levels of 0, 2, 6, and 18 mg/kg/day of p-Chloroaniline by oral gavage, 5 days a week for 103 weeks. Vehicle controls received deionized water by oral gavage. P-Chloroaniline was administered in aqueous hydrochloric acid.

Survival Analyses

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of p-Chloroaniline in male or female rats. See Tables 1 and 2 for mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Male rats had significant increasing trends in spleen fibrosarcomas, hemangiosarcomas, osteosarcomas, and combined sarcomas, all at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 18 mg/kg/day dose group with the controls for spleen fibrosarcomas, osteosarcomas, and combined sarcomas, all at $p < 0.01$.

Female rats had no significant increasing trends and no significant differences in the pair-wise comparisons of the dosed groups with the controls for tumors of the spleen.

These statistical analyses were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 3 and 4 for tumor analysis results.

The NTP statistical evaluation of the rat study further indicated increased incidences of adrenal pheochromocytomas in male and female rats. See Table A3, page 126, and Table B3, page 160, of the NTP report for the NTP analyses.

The same NTP report presented data analysis of a B6C3F₁ mouse study which indicated some evidence for a carcinogenic response in male mice (but no evidence in female mice). There were increased incidences of combined hepatocellular tumors and hemangiosarcomas of the liver and spleen. See Table C3, pages 190 - 192, of the NTP report for the NTP analyses.

The additional rat and mouse data referred to in the above NTP statistical analyses were not re-evaluated by current EPA methods because the splenic sarcomas of the male rat were more rare and occurred more frequently in the high dose group than any of the other tumors cited by NTP in either the rat or the mouse study.

Table 1. p-Chloroaniline - Charles River Fischer 344/N Rat Study
Male Mortality Rates⁺ and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	<u>Weeks</u>				Total
	1-26	27-52	53-78	79-105 ^f	
0	1/49	2/48	4/46	24/42	31/49 (63)
2	0/50	0/50	2/50	16/48	18/50 (36) ^{***}
6	0/50	2/50	3/46 ^a	11/43	16/48 (33) ^{***}
18	0/50	0/50	5/50	24/44 ^b	29/49 (59)

⁺Number of animals that died during interval/Number of animals alive at the beginning of the interval.

^aTwo accidental deaths at week 68, dose 6 mg/kg/day.

^bOne accidental death at week 99, dose 18 mg/kg/day.

^cNegative change from control.

^fFinal sacrifice at week 105.

() Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. p-Chloroaniline - Charles River Fischer 344/N Rat Study
Female Mortality Rates⁺ and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	<u>Weeks</u>				Total
	1-26	27-52	53-78	79-105 ^f	
0	1/50	3/49	7/46	12/39	23/50 (46)
2	1/50	0/49	1/49	9/48	11/50 (22) ^{***}
6	0/50	1/50	2/49	11/47	14/50 (28) ^{**}
18	0/50	0/50	3/50	10/47	13/50 (26) ^{**}

⁺Number of animals that died during interval/Number of animals alive at the beginning of the interval.

^fFinal sacrifice at week 105.

^{**}Negative change from control.

() Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 3. p-Chloroaniline - Charles River Fischer 344/N Rat Study

**Male Spleen Tumor Rates[†] and Exact Trend Test
and Fisher's Exact Test Results (p values)**

	<u>Dose (mg/kg/day)</u>			
	0	2	6	18
Fibrosarcomas (%)	0/46 (0)	1/50 (2)	2/48 (4)	17 ^a /50 (34)
p =	0.000 ^{**}	0.521	0.258	0.000 ^{**}
Hemangiosarcomas (%)	0/46 (0)	0/50 (0)	0/48 (0)	4 ^b /50 (8)
p =	0.004 ^{**}	1.000	1.000	0.069
Osteosarcomas (%)	0/46 (0)	0/50 (0)	1/48 (2)	19 ^c /50 (38)
p =	0.000 ^{**}	1.000	0.511	0.000 ^{**}
Combined (%)	0/46 (0)	1/50 (2)	3/48 (6)	38 ^d /50 (76)
p =	0.000 ^{**}	0.521	0.129	0.000 ^{**}

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

^aFirst fibrosarcoma observed at week 75, dose 18 mg/kg/day.

^bFirst hemangiosarcoma observed at week 89, dose 18 mg/kg/day.

^cFirst osteosarcoma observed at week 71, dose 18 mg/kg/day.

^dTwo animals in the 18 mg/kg/day dose group had both a fibrosarcoma and a hemangiosarcoma.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If ^{*}, then p < 0.05. If ^{**}, then p < 0.01.

Table 4. p-Chloroaniline - Charles River Fischer 344/N Rat Study

Female Spleen Tumor Rates⁺ and Exact Trend Test
and Fisher's Exact Test Results (p values)

	<u>Dose (mg/kg/day)</u>			
	0	2	6	18
Fibrosarcomas (%)	0/46 (0)	0/49 (0)	1 ^a /49 (2)	0/50 (2)
p =	0.742	1.000	0.516	1.000
Osteosarcomas (%)	0/46 (0)	0/49 (0)	0/49 (0)	1 ^b /50 (2)
p =	0.258	1.000	1.000	0.521
Combined (%)	0/46 (0)	0/49 (0)	1/49 (2)	1/50 (2)
p =	0.196	1.000	0.516	0.521

⁺Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.

^aFirst fibrosarcoma observed at week 105, dose 6 mg/kg/day.

^bFirst osteosarcoma observed at week 105, dose 18 mg/kg/day.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If ^{*}, then $p < 0.05$. If ^{**}, then $p < 0.01$.

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