

lab 13

1

Chronic Health Effects Testing

for

Hydroquinone

John L. O'Donoghue, V.M.D., Ph.D.

May 20, 1992

**Data Available From
Chemical Manufacturers Association**

TSCA Section 4 Test Rule

- **Neurotoxicity Study**
- **Teratogenicity Studies - Rats/Rabbits**
- **Two Generation Study - Rats**
- **Pharmacokinetics/Skin Absorption**

Discussion Points

- **The benzene literature is largely irrelevant for understanding the biological and biochemical consequences of HQ exposure.**
- **HQ is not an inducer or promotor of skin carcinogenesis.**
- **The kidney tumors seen following HQ ingestion are associated with renal toxicity and chronic progressive nephropathy.**
- **Mononuclear cell leukemia in female F-344 rats is not a reproducible effect indicative of carcinogenicity.**
- **The incidence of benign hepatocellular tumors in B6C3F₁ mice is questionable evidence of carcinogenicity.**
- **Clastogenicity studies with HQ are not relevant to predicting animal or human tumorigenicity.**
- **Metabolism plays an important role in understanding the biologic consequences of HQ exposure.**
- **The rate of HQ percutaneous absorption is relatively slow. Consequently, toxicity from dermal exposure is unlikely to occur.**
- **Additional research to address the issues raised by the NTP results is u y.**

Summary of primary neoplasms in F344/N rats and B6C3F₁ mice from a 2-year gavage study of hydroquinone (HNT, 1990)

Organ/tissue site	Rats		Organ/tissue site	Mice	
	Male	Female		Male	Female
Zymbal gland	+	+	Zymbal gland	+	+
Oral cavity	+	+	Lymphoma	+	+
Skin	+	-	Lung	+	+
			Harderian gland	+	±
			Mammary gland	-	+
			Preputial gland	+	NA
			Forestomach	±	±
			Ovary	NA	+
			Liver	-	±

Summary of primary neoplasms in F344/N rats and B6C3F₁ mice from a 2-year gavage study of hydroquinone (HNT, 1990)

Organ/tissue site	Rats		Organ/tissue site	Mice	
	Male	Female		Male	Female
Kidney	±	-	Liver	-	±
Mononuclear cell leukemia	-	±			

* response relative to vehicle controls (+) increase; (±) marginal increase; (-) no difference; (NA) not applicable

BENZENE DEPOSITION

431

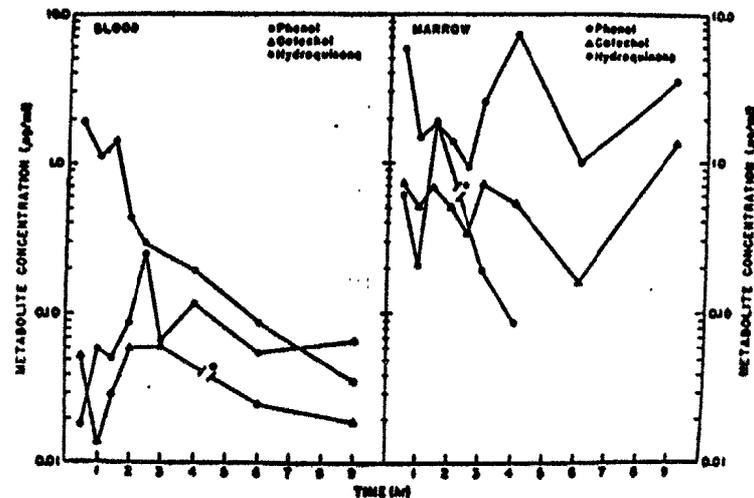
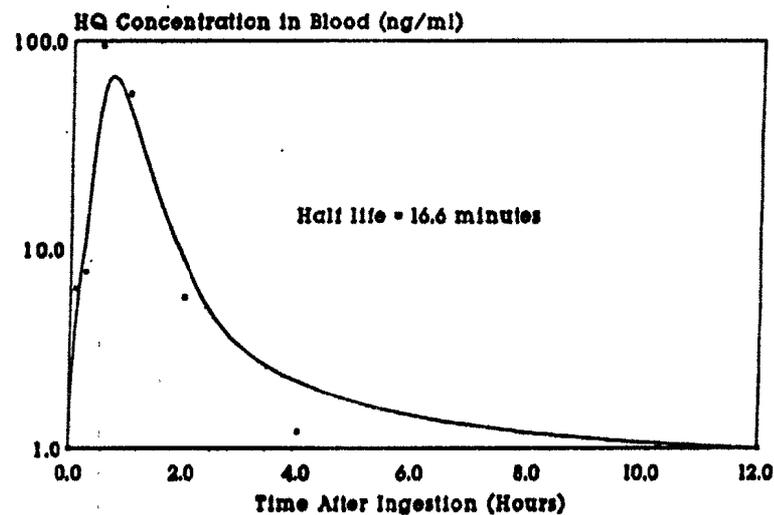


FIG. 2. Concentration of metabolites following a 6-hr inhalation exposure to benzene. Asterisks indicate points at which a compound was not determined or not detected due to technical difficulties. SE were all less than 50%. Each point is the mean for three animals.

Kinetics of Oral Hydroquinone (275 mg) in a Male Volunteer



HQ Dermal Bioassay in CR/HA Swiss Mice w/o Initiator

No./Fmls/Grp:	50	50	50
Initiator:	None	5µg Benzo[a]pyrene 3x/week	150µg Benzo[a]pyrene 1x/2wk prior to HQ
Vehicle:	Acetone	Acetone	Acetone
HQ Dose Levels:	5 mg	5 mg	5 mg
HQ Dose Freq.:	3x/week	3x/week	3x/week
Study Length: (weeks)	52	52	58
Results:	No tumors	HQ Weak Inhibitor 3 SQ Cell-HQ/BaP 10 SQ Cell-BaP	HQ Weak Inhibitor

Data from: VanDuuren and Goldschmidt (1976)

HQ Two-Year Bioassay (Oral Routes) - 1

	Carlson and Brewer (1953)	NTP (1989)	Shibata <i>et al.</i> (1991)
Species:	S-D Rats	F344 Rats/ B6C3F ₁ Mice	F344 Rats/ B6C3F ₁ Mice
No./Sex/Grp:	46-53 ¹	55	30
Route:	0.1, 0.25, 0.5, 1.0% HQ Diets	Gavage	0.8% HQ Diet
Dose Levels: (mg/kg/day)	Rats ~ 80-800 Mice	25 & 50 50 & 100	~ 360 ~ 1300
Dose Freq.: (day/week)	7	5	7
Study Length: (weeks)	Rats 104 Mice	103 103	104 96

¹ The 0.25% Group was 16-23 rats/sex/grp. Some rats were used for interim studies. Exposures included HQ (10 rats/sex/grp); HQ + 0.1% citric acid (16-23 rats/sex/grp); and HQ mixed in lard and heated to 190°C for 30 min (16-23 rats/sex/grp).

HQ Two-Year Bioassay (Oral Routes) - 2

	Carlson and Brewer (1953)	NTP (1989)	Shibata <i>et al.</i> (1991)
Rats			
Kidney Toxicity	None	Males/Females	Males/Females
Kidney Adenomas	None	Males	Males
Mononuclear Cell Leukemia	None	Females	None
Mice			
Kidney Hyperplasia		None	Males
Kidney Adenomas		None	Males (NS)
Liver Adenomas		Males (NS) ¹	Males
Liver Adenomas		Females	None

¹ Not significant when combined with carcinomas.

Number of Male Rats with Indicated Severity of Nephropathy (Adenomas) in the NTP Two-Year Gavage Study of Hydroquinone

Severity	Control	25 mg/kg	50 mg/kg
No. of rats examined	55	55	55
No nephropathy	2	3	0
Minimal	3	1	3
Mild	12	12 (1)	5
Moderate	26	31 (1)	15 (1)
Marked	12	8 (2)	32 (7)
Total No. Adenomas	(0)	(4)	(8)

Historical Control Incidence Range 0-6%

HQ Renal Toxicity - F-344 Rats

	NTP (1989)	NTP (1989)	NTP (1989)	Shibata <i>et al.</i> (1991)
No./sex/grp.:	10	10	55	30
Route:	Gavage in corn oil	Gavage in water	Gavage in water	0.8% HQ in diet
Dose Levels: (mg/kg/day)	25, 50, 100, 200, 400	25, 50	25, 50	~ 360
Dose Freq.: (days/week)	5	5	5	7
Study Length: (weeks)	13	65	103	104
Kidney weight:	ND	Inc. % BWT 50 mg/kg M	Inc. % BWT 50 mg/kg M	Inc. Abs. & % BWT - M Inc. % BWT - F
Urinalysis:	ND	ND	ND	ND
Histopathology: (nephropathy)	200 mg/kg: 7/10 M 6/10 F 100 mg/kg: 1/10 F	Inc. Severity 50 mg/kg: 6/10 M 25 mg/kg: 5/5 M	Inc. Severity 50 mg/kg: 20/55 M	Inc. Severity M: 14/30 F: 7/30 (minimal)

HQ Renal Toxicity - S-D and Carworth Rats

	Topping <i>et al.</i> (1988)	Carlson and Brewer (1953)	Christian <i>et al.</i> (1976)	Christian <i>et al.</i> (1976)
Strain:	S-D	S-D	Carworth	Carworth
No./sex/grp.:	10	46-53 ¹	6	20
Route:	Gavage in water	0.1, 0.25, 0.5, 1.0% HQ Diets	2.5, 5, 10 g/L in water	1, 2, 4 g/L in water
Dose Levels: (mg/kg/day)	20, 64, 200	~ 80-800	230 - 810	110- 430
Dose Freq.: (days/week)	5	7	7	7
Study Length: (weeks)	13	104	8	15
Kidney weight:	No effect	ND	Inc. @ 5 and 10 g/L	Inc. Rel. Wt. 1, 2, 4 g/L (1 g/L F NS)
Urinalysis:	ND	ND	ND	ND
Histopathology:	No effect	No effect	No effect	No effect

¹ The 0.25% Group was 16-23 rats/sex/grp. Some rats were used for interim studies. Exposures included HQ (10 rats/sex/grp); HQ + 0.1% citric acid (16-23 rats/sex/grp); and HQ mixed in lard and heated to 190°C for 30 min (16-23 rats/sex/grp).

HQ Renal Toxicity - B6C3F₁ Mice

	NTP (1989)	NTP (1989)	NTP (1989)	Shibata <i>et al.</i> (1991)
No./sex/grp.:	10	10	55	30
Route:	Gavage in corn oil	Gavage in water	Gavage in water	0.8% HQ in diet
Dose Levels: (mg/kg/day)	25, 50, 100, 200, 400	50, 100	50, 100	- 1300
Dose Freq.: (days/week)	5	5	5	7
Study Length: (weeks)	13	65	103	96
Kidney weight:	ND	Inc. % BWT 50 and 100 mg/kg F	No effect	Inc. % BWT Females only
Urinalysis:	ND	ND	ND	ND
Histopathology:	No effect	No effect	No effect	Tubular Hyperplasia in 9/30 males

HQ Renal Toxicity - Mixed-Breed Dogs

	1	2	5 males
No./Dogs/Grp.:			
Route:	Oral Tablet	Oral Tablet	Oral Tablet
Dose Levels: (mg/kg/day)	16	1.6 and 40	100
Dose Freq.: (days/week)	7	7	7
Study Length: (weeks)	80	1.6 mg/kg for 31 wks +40 mg/kg for 49 wks	26
Kidney Weight:	ND	ND	ND
Urinalysis:	No effect	No effect	No effect
Histopathology:	No effect	No effect	No effect

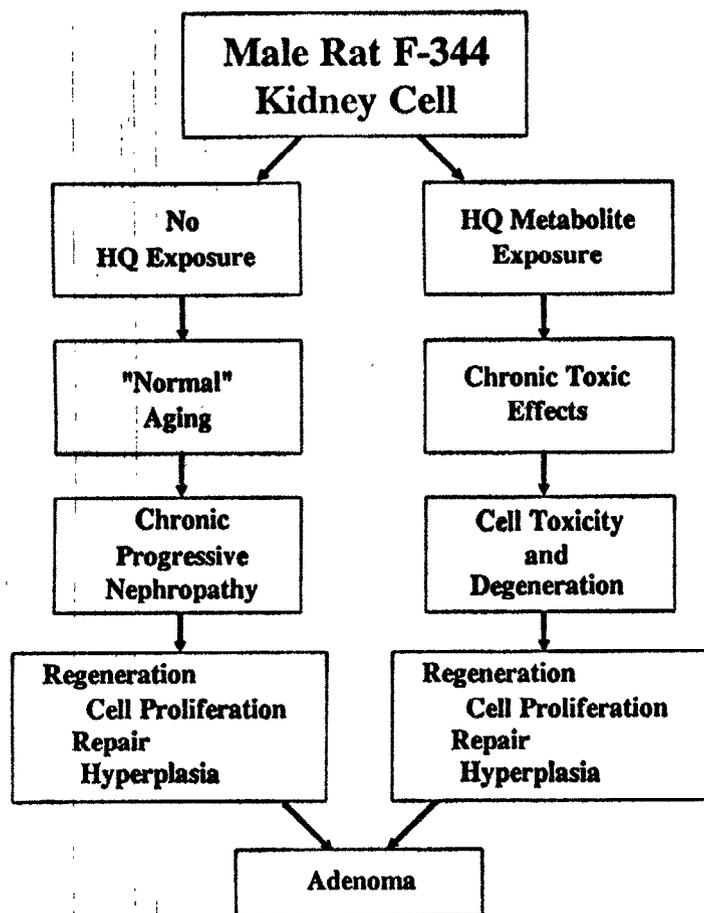
Data from Carlson and Brewer, 1953

HQ Renal Toxicity - Human

Subjects:	2 males	17 males/females
Route:	Oral 3 divided doses with meal	Same
Dose Levels: (mg/day)	500	300
Dose Freq.: (days/week)	7	7
Study Length: (weeks)	20	12-20
Urinalysis:	No effect	No effect

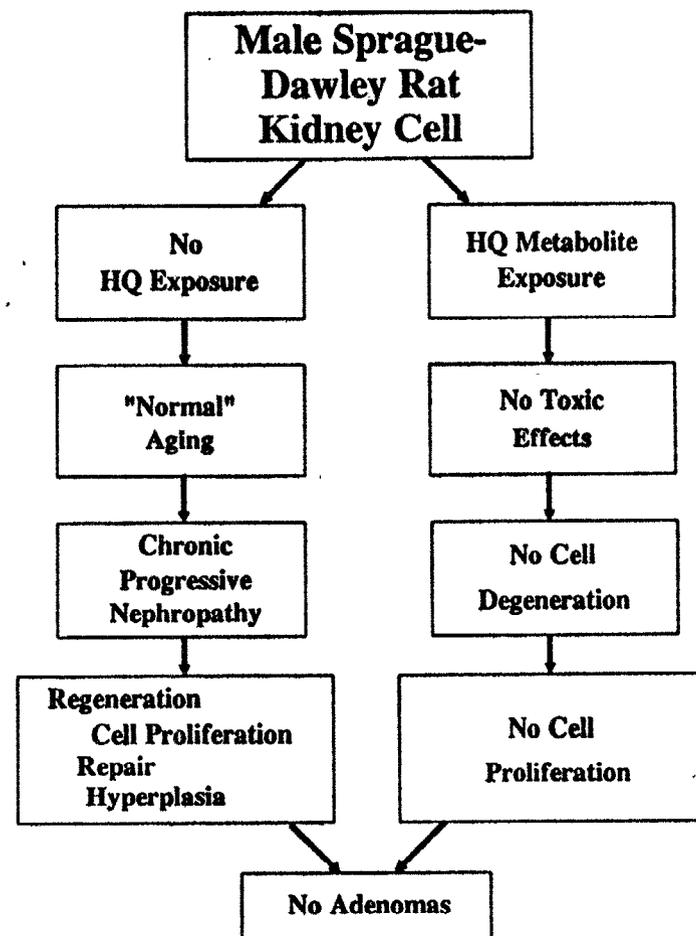
Data from Carlson and Brewer, 1953

**Proposed Interaction Between
CPN-induced and HQ-induced
Cell Hyperplasia in the Male F-344 Rat**



Similar interactions are not expected to occur in female F-344 rats, SD rats, or other species.

**Hydroquinone Exposure Does Not Result
In Kidney Toxicity or Adenomas In
Male Sprague-Dawley Rats**



Mononuclear Cell Leukemia in Female F344 Rats - 1

	NTP Historical Control ¹	NTP Bioassay (1989)			Shibata <i>et al.</i> (1991)	
		0 mg/kg	25 mg/kg	50 mg/kg	0 mg/kg	360 mg/kg
No. Tumors	75/299 ²	9/55	15/55 ⁴	22/55 ⁴	6/30	8/30
Incidence (%)	25 ± 15 ³	16	27	40	20	26

¹ NTP Water Gavaged Female F344 Rats

² No. Tumors/No. Animals

³ Mean ± SD

⁴ Statistically Significant Trend

Mononuclear Cell Leukemia in Female F344 Rats - 2

- Incidence in HQ treated rats was within historical control limits.
- Only the 50 mg/kg group was statistically significant.
- 15 month NTP animals had no leukemias.
- Male F344 rats and B6C3F₁ mice (M and F) in NTP study did not differ from control in leukemia incidence.
- Mononuclear cell leukemia in female F344 is increasing in NTP studies.
- Shibata *et al.* results did not support NTP results.

Hepatocellular Adenomas in B6C3F₁ Mice - 1

	NTP Historical Control ¹	NTP Bioassay (1989)			Shibata <i>et al.</i> (1991)	
		0 mg/kg	50 mg/kg	100 mg/kg	0 mg/kg	~1300 mg/kg
Females						
No. Tumors	22/348 ²	2/55	15/55 ⁴	12/55 ⁴	0	1/30
Incidence (%)	6 ± 5 ³	4	27	22	0	3
Males						
No. Tumors	54/347	9/55	21/55 ^{4,5}	20/55 ^{4,5}	6/27	14/30 ⁴
Incidence (%)	16 ± 4	16	39	36	22	47

¹ NTP Water Gavaged B6C3F₁ Mice

² No. Tumors/No. Animals

³ Mean ± SD

⁴ Statistically Significant for Adenomas

⁵ Statistically Significant Negative Trend for Carcinomas

Hepatocellular Adenomas in B6C3F₁ Mice - 2

- NTP and Shibata *et al.* results are inconsistent.
- B6C3F₁ hepatic carcinomas were not increased.
- Rats did not show corresponding results.
- No clear dose response.

Discussion Points

- The benzene literature is largely irrelevant for understanding the biological and chemical consequences of HQ exposure.
- HQ is not an inducer or promotor of skin carcinogenesis.
- The kidney tumors seen following HQ ingestion are associated with renal toxicity and chronic progressive nephropathy.
- Mononuclear cell leukemia in female F-344 rats is not a reproducible effect indicative of carcinogenicity.
- The incidence of benign hepatocellular tumors in B6C3F₁ mice is questionable evidence of carcinogenicity.
- Clastogenicity studies with HQ are not relevant to predicting animal or human tumorigenicity.
- Metabolism plays an important role in understanding the biologic consequences of HQ exposure.
- The rate of HQ percutaneous absorption is relatively slow. Consequently, toxicity on dermal exposure is unlikely to occur.
- Additional research to address the issues raised by the NTP results is underway.

Conclusion

- The available data should not present a concern for chronic health effects from HQ exposures.
- Additional research is underway or planned to address questions raised by the NTP bioassay.