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HYDROQUINONE
CAS N°: 123-31-9

SIDS INITIAL ASSESSMENT PROFILE

CAS Nr.	123-31-9
Chemical Name	Hydroquinone (1,4-Benzenediol)
Structural formula	

CONCLUSIONS AND RECOMMENDATIONS

It was reported that the chemical was of low international concern, but processing sites such as in industrial photography, may present local environmental concern based on default modelling.

It is currently considered of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Virtually all the uses of hydroquinone are industrial. Approximately 25% of the hydroquinone manufactured is used as an intermediate for synthesis of antioxidants and antiozonants for use in rubber. Another 25% is used as an intermediate for chemical conversion to inhibitors used to stabilize monomers. An additional 33% is used in the photographic industry including black-and-white photographic film, lithography, and hospital x-ray film. Other uses (11-12%) include chemical conversion to stabilizers for paints, varnishes, motor oils, and fuels, and for antioxidants for industrial fats and oils. Hydroquinone has been used in water cooling towers as a rust inhibitor. Hydroquinone is considered to be readily biodegradable and photodegradable.

The aquatic toxicity of hydroquinone to fresh water fish, *Daphnia*, and algae was between 0.050-0.335 mg/l; the predicted chronic values for these fresh water taxa were calculated to be < 0.100. The 84 hr LC₅₀ for the salt water shrimp, *C. septemspinosa*, was selected as the only salt water species for analysis. Based on these data and on the predicted aquatic toxicity values, the USEPA identified concern concentrations or predicted no effect concentrations (PNECs) at 1.0 µg/l for fresh water species and 8.0 µg/l for salt water species. Alternatively, a PNEC can be derived using the assessment factors recommended in the SIDS Manual. As only acute effect data for fish and daphnids are available, an assessment factor of 100-1000 would be appropriate. Due to the large available database, a factor of 100 would be acceptable. Applied to the lowest experimental value of 0.044 mg/l (fathead minnow), a PNEC of 0.44 µg/l can be derived.

The PNECs are compared to the maximum annual estimated water concentrations based on the 1992 TRI release levels and the "what-if scenarios" for manufacturing, processing, and use sites which were considered to be conservative estimates of PECs.

All but one of the direct discharge sites have PECs less than 0.07 µg/l and, therefore, the PEC/PNEC ratios range from 8.2×10^{-5} to 6.8×10^{-2} using a PNEC of 1.0 µg/l. One direct discharger has a predicted surface water concentration of 180 µg/l which would indicate a PEC/PNEC ratio of greater than one. However, in investigating site specific information for this discharger, it became apparent that the plant PEC/PNEC ratio was significantly less than 1 as no hydroquinone was

detected from its NPDES-regulated outfall prior to discharge.

Use of the alternative PNEC of 0.44 µg/l causes an additional four indirect discharges to exceed a PEC/PNEC ratio of one (PEC/PNEC ratios of 1.5-2.0); however, considering that there are estimated to be 16,000 to 66,000 processor/users of hydroquinone in the USA, the number of predicted PEC/PNEC ratios > 1 are small. Since all of the direct and indirect discharges identified in the exposure assessment have NPDES regulated discharges, it is very unlikely that they actually have discharges with PEC/PNEC ratios > 1. It is much more likely that the "what-if scenario" has overestimated the actual PEC.

The frequency of exceeding a PEC/NPEC of 1 can be calculated using the Probabilistic Dilution Model (PDM 3) program. Using this model, a concern concentration of 1 µg/l is predicted to be exceeded 0.5 days/yr (0.14% of the year) and a concern level of 0.044 µg/l is predicted to be exceeded 3 days/yr (0.81% of the year).

While toxicity to mammalian species is associated with high doses of hydroquinone, these effects are either species- and strain-specific or minimized in humans through reduced exposure. Dermal effects in humans who use hydroquinone-containing skin products appear to be limited to individuals who misuse the products or to products which contain other active ingredients. Similar dermal effects have not been demonstrated in animals treated with similar or higher concentrations of hydroquinone. Potential hazards from dermal exposure to aqueous solutions of hydroquinone are also low based on dermal absorption rates. Exposure information provided indicates that exposure potential for hydroquinone is low. Because no human health concerns have been identified and exposure potential is low, this substance has a low priority for further work.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

Depending on the extent of use, national action to avoid risk to the aquatic environment could be warranted on some site-specific conditions.

SIDS SUMMARY**Hydroquinone**

CAS NO: 123-31-9		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			169 °C
2.2	Boiling Point			286 °C
2.3	Density			1.341 kg/m ³
2.4	Vapour Pressure			2.34 x 10 ⁻³ Pa at 25°C
2.5	Partition Coefficient (log P _{ow})		Calculated	0.50-0.61
2.6A	Water Solubility			73000 mg/L at 25°C
2.6B	pH pKa			4.0 - 4.7 pK ₁ = 9.9
2.12	Oxidation:Reduction Potential			+286 mV at 25°C and pH 7
ENVIRONMENTAL FATE/BIODEGRADATION				
3.1.1	Photodegradation		Calculated	In air T _{1/2} = < 5 weeks
3.1.2	Stability in water		OECD 111	T _{1/2} = 111 hrs at pH 7
3.2	Monitoring data		NA	In air = ND* In surface water = ND In soil/sediment = ND In biota = ND
3.3	Transport and Distribution		Calculated (Fugacity level I)	In Air 0.21% In Water 99.6% In Sediment 0.06% In Soil 0.01% In Biota < 0.001%
3.5	Biodegradation		Similar to OECD 301D	readily biodegradable

* ND = None detected.

CAS NO: 123-31-9		SPECIES	PROTOCOL	RESULTS
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	Pimephales promelas Brachydanio rerio	Similar to OECD 203	LC ₅₀ (96 hr) = > 0.4 mg/L LC ₅₀ (96 hr) = 0.17 mg/L
4.2	Acute/Prolonged Toxicity to Aquatic Invertebrates Daphnia	Daphnia magna	Similar to OECD 202	LC ₅₀ (24 hr) = 0.09 mg/L LC ₅₀ (24 hr) = 0.12 mg/L LC ₅₀ (96 hr) = 0.05 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	Selenastrum capricornutum	Similar to OECD 201	LC ₅₀ (7 d) = 1-4 mg/L NOEC = 0.4 mg/L
4.5.2	Chronic Toxicity to Aquatic Invertebrates (Daphnia)	-	-	-
4.6.1	Toxicity to Soil Dwelling Organisms	-	-	-
4.6.2	Toxicity to Terrestrial Plants	Ryegrass Radish Lettuce	ASTM STP 1091	NOEC = 10 mg/L
		Corn Marigold Lettuce Radish	Similar to OECD 208	NOEC (corn) = 100 mg/L NOEC = 10 mg/L
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)	Pigeon	other	LD ₅₀ = 500 mg/kg

CAS NO: 123-31-9		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat (?) Rat (Osborne-Mendel) Rat (Wistar) Rat (Sprague) Mouse (?) Mouse (Swiss)	Similar to OECD 401	LD ₅₀ = 390 mg/Kg LD ₅₀ = 302 mg/Kg LD ₅₀ = 298 mg/Kg LD ₅₀ = 323 mg/Kg LD ₅₀ = 680 mg/Kg LD ₅₀ = 390 mg/Kg
5.1.2	Acute Inhalation Toxicity	-	-	-
5.1.3	Acute Dermal Toxicity	Guinea pig (?)	Similar to OECD 402	LD ₅₀ = > 1000 mg/Kg
5.4	Repeated Dose Toxicity	Rat (Sprague) Rat (F-344) Mouse (B6C3F1) Rat (F-344) Mouse (B6C3F1) Rat (F-344)	USEPA TSCA 40 CFR 798.6050 other other other other Similar to OECD 411	NOEL (oral) = 20 mg/Kg (13 w) NOEL (dermal) = 1920 mg/Kg (14 d) NOEL (dermal) = 4800 mg/Kg (14 d) NOEL (oral) < 25 mg/Kg (13 w) NOEL (oral) < 25 mg/Kg (13 w) NOAEL (dermal) = 74 mg/Kg (13 w)
5.5 A	Genetic Toxicity in Vitro Bacterial Test (Gene Mutation)	Salmonella typhimurium	Similar to OECD 471	Negative (with metabolic activation) Negative (without metabolic activation)
B	Non-Bacterial in Vitro Test (Chromosomal aberrations)	Chinese Hamster Ovary	Similar to OECD 473	Positive (with metabolic activation) Negative (without metabolic activation)
5.6	Genetic Toxicity in Vivo	Mouse (CD-1)	Similar to OECD 474	Positive (ip injection) Weak (oral gavage)
5.8	Toxicity to Reproduction	Rat (Sprague)	OECD 416	NOEL = 15 mg/Kg (General toxicity) NOEL = 150 mg/Kg (Repro. Tox. parental) NOEL = 150 mg/Kg (Repro. Tox. F1)
5.9	Developmental Toxicity/ Teratogenicity	Rat (Sprague) Rabbit (NZW)	OECD 414 OECD 414	NOEL = 100 mg/Kg (General toxicity) NOEL = 300 mg/Kg (Pregnancy/litter) NOEL = 300 mg/Kg (Foetal data) NOEL = 25 mg/Kg (General toxicity) NOEL = 75 mg/Kg (Pregnancy/litter) NOEL = 75 mg/Kg (Foetal data)
5.11	Experience with Human Exposure	NA	NA	Less than 100 workers are potentially exposed during manufacture. One report (1947) attributes eye injury to vapors of quinone or hydroquinone. No other reports have demonstrated hydroquinone-related effects. Non-industrial exposure occurs in consumers using nonprescription drugs containing 2% hydroquinone and photohobbyists that develop black-and-white film.

COVER PAGE

SIDS Initial Assessment Report (SIAR)

Chemical Name: **Hydroquinone**

CAS No.: **123-31-9**

Sponsor Country: **United States of America**

SIDS Contact Point
in Sponsor Country: **Mr. Charles Auer**

HISTORY:

SIDS Dossier and Testing Plan were reviewed at the 3rd SIDS Review Meeting, September 1993. Agreed that no tests were needed. At the SIAM 3, this chemical was identified as having a potential concern due to widespread consumer exposure and reports of skin whitening from mis-use. It was recommended to gather exposure information. After the SIAM, some additional information on this chemical was gathered using the proposed OECD format. The SIDS Initial Assessment Report, with any changes, as appropriate, to the conclusion and recommendations, were reviewed and discussed at SIAM 4.

Following SIAM 4 in Tokyo on 20-22 May 1996, additional environmental modeling information for hydroquinone use at specific sites was submitted by the French representative. This information was incorporated into the final SIAR document.

COMMENTS:

The submitted information confirmed the SIAR presented at SIAM 3 and SIAM 4 and has been revised to include additional information collected following the SIAM 4 meeting. The recommendation continues to be low priority for further work.

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

Chemical name: 1,4-Benzenediol

Synonyms: Hydroquinone
para-Dihydroxybenzene
para-Benzenediol
I-Hydroquinone

CAS number: 123-31-9

Empirical formula: $C_6H_6O_2$

Structural formula:



Molecular weight: 110.11

Degree of purity: > 99%

Major impurities: < 1% water

Essential additives: none

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production Volume

Production is estimated at 35000 tonnes per year worldwide in 1992 (IPCS, 1994). Production in the U.S.A. was 18700 - 20900 tonnes per year in 1992 (U.S.E.P.A., 1995). Hydroquinone is manufactured in the U.S.A., Japan, France, Italy, China, and Canada. Eastman Chemical Company, the major producer of hydroquinone in the U.S.A., is located in Kingsport, Tennessee. Hydroquinone is produced at a single site in Canada at 0.1 - 1 tonne per year (Taylor, 1995).

2.2 Production Processes

There are three current manufacturing processes for hydroquinone: oxidative cleavage of diisopropylbenzene, oxidation of aniline, and hydroxylation of phenol.

At Eastman Chemical Company, diisopropyl benzene is air oxidized to the intermediate diisopropylbenzene bishydroperoxide. This hydroperoxide is purified by extraction and reacted

further to form hydroquinone. Process solvents are recycled. Water-insoluble impurities are incinerated, and the two water-based impurity streams are biodegraded in the plant wastewater treatment system. The purified product is isolated by filtration, and packaged. The process is almost entirely closed, continuous, computer-controlled, and monitored.

Hydroquinone can also be prepared by oxidizing aniline to quinone in the presence of manganese dioxide and sulfuric acid. Quinone is then reduced to hydroquinone using iron oxide. The resulting hydroquinone is crystallized and dried. The process occurs in a closed system.

Hydroquinone is also manufactured by hydroxylation of phenol using hydrogen peroxide as a hydroxylation agent. The reaction is catalyzed by strong mineral acids, or ferrous or cobalt salts.

2.3 Uses and Functions

Virtually all the uses of hydroquinone are industrial. Approximately 25% of the hydroquinone manufactured is used as an intermediate for synthesis of antioxidants and antiozonants for use in rubber. Another 25% is used as an intermediate for chemical conversion to inhibitors used to stabilize monomers. An additional 33% is used in the photographic industry including black-and-white photographic film, lithography, and hospital x-ray film. Other uses (11-12%) include chemical conversion to stabilizers for paints, varnishes, motor oils, and fuels, and for antioxidants for industrial fats and oils. Hydroquinone has been used in water cooling towers as a rust inhibitor.

About 0.05% of the hydroquinone manufactured is used in skin lightening creams. Hydroquinone is also used as a coupler in oxidative hair dyes. Small amounts of hydroquinone are used by photohobbyists for the development of black-and-white films and paper.

2.4 Form of Marketed Products

Hydroquinone is sold by manufacturers as a dry, crystalline solid packaged in plastic film lined sacks or drums. For photographic purposes, hydroquinone is sold in powder formulations or in aqueous solution (concentrated pre-mixes are 1-10% while working strength solutions are 0.5-3%). Rust inhibitors may contain <1% hydroquinone in a powder mixture. Polymerization inhibitors may contain <1% hydroquinone in solution or dry powder. Skin lightening formulations which are sold as non-prescription drugs contain 2% hydroquinone in a hydroalcoholic cream.

2.5 Sources of Release to the Environment

Hydroquinone is a naturally occurring substance found in several foods (e.g., wheat products, fruits) and beverages (e.g., brewed coffee, some teas, beer, red wine) (Deisinger *et al.*, 1996). Hydroquinone is formed as a byproduct of metabolism in several bacteria and marine species. It is estimated that approximately 5×10^4 kg of hydroquinone is generated per year during cigarette smoking.

During manufacture, hydroquinone is potentially released to the air, water, soil, or other sites (e.g., waste water treatment works). Data from the 1992 Toxic Release Inventory (TRI, 1992) reported to the U.S.E.P.A. indicated that 4215 kg was released to the air (35% of total) or off-site (65% to waste water treatment facilities and an unidentified off-plant site). The TRI releases are approximately 0.02% of the total amount of hydroquinone manufactured in the U.S.A.

Hydroquinone is processed or used by an estimated 16000 - 66000 facilities in the U.S.A. 1992 TRI releases from processing and use operations were 216000 kg/yr or 1.0-1.2% of the total amount

produced. TRI releases by processor/users were 2% to air, 1% to water, 53% to land, and 44% off-site including waste water treatment works. Hydroquinone releases to the environment in Canada during 1993 were reported by four facilities to be a total of 0.153 tonnes/yr into an unspecified environmental compartment(s) (Taylor, 1995).

Releases in other countries are assumed to be at equivalent levels.

Releases of hydroquinone may occur during drumming/bagging operations which are typically conducted in protected but not totally closed systems. Releases may also occur during cleaning and maintenance.

During processing and use, hydroquinone exposure may occur during the opening and dumping of bags and drums into hoppers, reactors, or mixing vessels. Bags are typically opened and emptied manually while drums are typically opened and their plastic liners slit manually, and then dumped with mechanical lifting devices. Releases during processing typically occur over periods of 10-60 minutes, one-four times/day.

Hydroquinone should not volatilize from photoprocessing solutions because of its water solubility, very low vapor pressure, and high vapor density. Thus potential exposure during photoprocessing is limited to mixing operations where dry powder formulations containing hydroquinone are added to water to make working-strength solutions. Hydroquinone present in developers for black-and-white and x-ray films can appear in the diluted effluent from photoprocessing. The amount of hydroquinone in the effluent depends on its concentration in the original developing solution, the photodeveloper replenishment rate, and the volume of waste waters. The hydroquinone content of fresh working solutions is ca. 0.5-2.5% (w/v).

2.6 Material Safety Data Sheet Information on Safe Handling

The following information is provided from an Eastman Chemical Company MSDS for hydroquinone.

HMIS Hazard Ratings: Health - 2, Flammability - 1, Chemical reactivity - 0.

NFPA Hazard Ratings: Health - 2, Flammability - 1, Chemical reactivity - 0.

NOTE: HMIS and NFPA ratings involve data and interpretations that may vary. They are intended only for rapid, general identification of the magnitude of the specific hazard. To deal adequately with the safe handling hydroquinone, all the information contained in the MSDS must be considered.

First-Aid Measures

Inhalation: Move to fresh air. Treat symptomatically. Get medical attention if symptoms persist.

Eyes: Immediately flush with plenty of water for at least 15 minutes. If easy to do, remove contact lenses. Get medical attention.

Skin: Immediately remove contaminated clothing and shoes and wash skin with soap and plenty of water. If skin irritation or an allergic skin reaction develops, get medical attention. Wash contaminated clothing before reuse. Destroy or thoroughly clean contaminated shoes.

Ingestion: Call a physician or poison control center immediately. Induce vomiting as directed by medical personnel. Never give anything by mouth to an unconscious person.

Fire Fighting Measures

Extinguish Media: Water spray, dry chemical.

Special fire-Fighting Procedures: Wear self-contained breathing apparatus and protective clothing.

Hazardous Combustion Procedures: Carbon dioxide, carbon monoxide.

Unusual Fire and Explosion Hazards: Powdered material may form explosive dust-air mixtures.

Accidental Release Measures

Sweep up and place in a container for chemical waste.

Handling and Storage

Personal Precautionary Measures: Avoid contact with eyes, skin, and clothing. Avoid breathing dust. Do not taste or swallow. Use only with adequate ventilation. Wash thoroughly after handling. Regular cleaning of working surfaces, gloves, etc., will help minimize the possibility of a skin reaction.

Prevention of Fire and Explosion: Keep from contact with oxidizing materials. Minimize dust generation and accumulation. Refer to NFPA Pamphlet No. 654, "Prevention of Fire and Dust Explosions in the Chemical, Dye, Pharmaceutical, and Plastics Industries."

Storage: Keep container closed.

Exposure Controls/Personal Protection

Exposure Limits:

ACGIH Threshold Limit Value (TLV): hydroquinone: 2 mg/m³ 8-hr TWA.

OSHA (U.S.A.) Permissible Exposure Limit (PEL, 1989 Table Z-1-A values or section-specific standards: hydroquinone: 2 mg/m³ TWA.

Ventilation: Good general ventilation (typically 10 air changes per hour) should be used. Ventilation rates should be matched to conditions. Use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits.

Respiratory Protection: If engineering controls do not maintain airborne concentrations below recommended exposure limits, an approved respirator must be worn. Respirator type: dust. If respirators are used, a program should be instituted to assure compliance with OSHA Standard 29 CFR 1910.134.

Eye Protection: Wear safety glasses with side shields (or goggles) and a face shield. Wear a full-face respirator, if needed.

Skin Protection: Wear chemical-resistant gloves, boots, and protective clothing appropriate for the risk of exposure.

Recommended Decontamination Facilities: Eye bath, washing facilities, safety shower.

Physical and Chemical Properties (Properties not provided elsewhere in SIAR.)

Odor: odorless

Odor Threshold: not applicable

Flash Point (closed cup): 165°C (329°F)

Lower Explosive Limit: not available

Upper Explosive Limit: not available

Autoignition Temperature (ASTM D 2155): 499°C (930°F)

Sensitivity to Mechanical Impact: insensitive at 550 inch-pounds

Sensitivity to Static Discharge: not available

Stability and Reactivity

Stability: Stable.

Incompatibility: Material can react with strong oxidizing agents.

Hazardous Polymerization: Will not occur.

Disposal Considerations

Discharge, treatment, or disposal may be subject to national, state, or local laws. Incinerate. Since emptied containers retain product residue, follow label warnings even after container is emptied.

Transport Information

DOT (U.S.A.) Status: regulated

Class 6.1, packing group III

TDG (Canada) Status: regulated

Class 6.1, packing group III

Air - International Civil Aviation Organization (ICAO)

ICAO Status: regulated

Class 6.1, packing group III

Sea - International Maritime Dangerous Goods (IMDG)

IMDG Status: regulated

Class 6.1, packing group III

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

Exposure relevant properties:

Water solubility:	73 g/L at 25°C
Partition coefficient log P _{ow} :	0.50-0.61
Vapor pressure:	2.34 x 10 ⁻³ Pa at 25°C
BOD ₅	1.00 g O ₂ /g
COD ₅	1.83 gO ₂ /g
BOD ₅ /COD ₅	0.55

- Degradation:

Hydroquinone degrades by both biotic and abiotic mechanisms. Biodegradation is affected by pH, temperature, aerobic/anaerobic conditions, and acclimation of the microorganisms involved (Devillers *et al.*, 1990).

Under aerobic conditions, Harbison and Belly (1982) reported that 74% of the radioactivity from the incubation of activated sludge and ¹⁴C-hydroquinone was recovered as carbon dioxide in 5-10 days. Small amounts of 1,4-benzoquinone, 2-hydroxy-1,4-benzoquinone, and β-ketoadipic acid are formed as metabolites of hydroquinone. A maximum concentration of 0.11% (1.05 mg/L) 1,4-benzoquinone was detected at 2 hr during incubation of 950 mg/L hydroquinone by yeast cultures (Harbison and Belly, 1982). At later time points 1,4-benzoquinone levels were lower and benzoquinone was not detected in the effluent from the activated sludge unit. Gerike and Fischer (1979) reported that 82% of hydroquinone was converted to CO₂ in a 28-day Sturm test and that 97% of the dissolved organic carbon was removed in 28 days. Thus hydroquinone is primarily converted to CO₂ or mineralized during aerobic degradation.

Under anaerobic conditions, hydroquinone is metabolized through phenol, instead of 1,4-benzoquinone, prior to mineralization (IPCS, 1994).

As the organisms which biodegrade hydroquinone are widely distributed in the environment in sludges, soils, sediments, and composts (Devillers *et al.*, 1990), hydroquinone is expected to readily biodegrade in soils and water.

Due to its intrinsic properties, hydroquinone is relatively rapidly photodegraded; phototransformations may occur from direct excitation or from induced or photocatalytic reactions (IPCS, 1994).

- Bioaccumulation:

With measured partition coefficients log P_{ow} = 0.50-0.61, hydroquinone is not considered to undergo bioaccumulation (IPCS, 1994). Bioaccumulation factors of 40 have been determined for algae and fish (Freitag *et al.*, 1985).

- Distribution between environmental compartments and occurrence in the environment:

The environmental transport of hydroquinone can be partially predicted based on its physical-chemical properties. With a melting point of 169°C, a vapor pressure of 2.34×10^{-3} Pa at 25°C and a relative vapor density of 3.81 (air=1), it is not expected to transport into the atmosphere. A calculation of fugacity using Mackay's model I indicates that hydroquinone will be distributed to the water compartment (99.6%) when released into the environment.

(i) Air

Hydroquinone is essentially non-volatile in its solid form. Its solubility in water (which increases with temperature), low vapor pressure, and high relative vapor density, and low Henry's law constant (3.84×10^{-11} atm-m³/mole; Meylan and Howard, 1991) indicate that hydroquinone will not evaporate from water into the atmosphere. The half-life of hydroquinone in the air is 14 hr (U.S.E.P.A., 1990)

In its dry solid form, hydroquinone is stable and darkens only slowly if exposed to the air. In the presence of moisture and ambient levels of oxygen, hydroquinone can undergo oxidation to 1,4-benzoquinone which is more likely to volatilize because of its higher vapor pressure. As this potential reaction is well recognized, manufacturing plants do not let hydroquinone powders stand in open environments prior to bagging or drumming operations. For the same reason, hydroquinone-containing products such as photographic developers contain stabilizers such as sodium sulfite to prevent or retard oxidation.

(ii) Water

Due to its physical chemical properties, hydroquinone can be expected to partition to the water compartment. As its melting point is 169°C, vapor pressure is low, Henry's law constant is relatively low, and its solubility in water increases with temperature, hydroquinone is not likely to be volatilized to the air compartment from water. In waste water, hydroquinone would be expected to be readily biodegradable. If hydroquinone were present in an open body of water, it would be expected to both biodegrade and photodegrade. Hydroquinone half-life in surface water is 20 hr (U.S.E.P.A., 1990). While 1,4-benzoquinone would be expected to be one of the degradation products of hydroquinone, its ready degradation (Harbison and Belly, 1982) would not be expected to impact the toxicity of a hydroquinone release. Releases of 1,4-benzoquinone itself to water are small and decreasing. TRI data indicate the following total releases of 1,4-benzoquinone to the water environment in the U.S.A.: 50 kg/yr (1987), 64 kg/yr (1988), 5.5 kg/yr (1989), 2.3 kg/yr (1990), 0 kg/yr (1991), and 1.8 kg/yr (1992). These data suggest that there is unlikely to be a significant additivity of effect between water releases of hydroquinone and 1,4-benzoquinone.

(iii) Soil

Hydroquinone released to the soil would be expected to mineralize as organisms which can degrade hydroquinone are commonly found in soils and compost. Half-life in soil is 2-14 days and depends on photo-oxidation and bacterial degradation (U.S.E.P.A., 1990). Hydroquinone present in soil could be expected to partition to water in the soil and be mobile. Half-life values in ground water are 4-14 days (aerobic conditions) and up to a month (anaerobic conditions) (U.S.E.P.A., 1990). However, hydroquinone and its immediate degradation product, 1,4-benzoquinone may also be absorbed to the soil. Since hydroquinone and 1,4-benzoquinone are electron donor and electron acceptor molecules respectively, they could form charge transfer complexes with soil particles. Hydroquinone and its biodegradation products may contribute to the formation of humic acids which are polymerization products of polyphenols commonly formed during the biodegradation of

plants. Much of the naturally occurring hydroquinone in plants may be reincorporated into soils in this manner.

3.1.2 Predicted Environmental Concentrations

Estimates of predicted environmental concentrations (PEC) from hydroquinone manufacturing, processing, and use are based on 1992 TRI data reported to the U.S.E.P.A. (1995). These "what-if scenarios" estimate the hydroquinone concentration in air and water using simple, conservative atmospheric dispersion models (EAB, 1994; Versar, 1992a). Surface water concentrations were estimated using site-specific receiving stream flow data and a simple dilution model. These "what-if scenarios" have been developed to assess potential exposure under a set of hypothetical conditions or under a set of conditions for which actual exposure parameter data are incomplete or non-existent. The calculated PECs are not intended to provide information about how likely the combination of exposure parameter values might be in the actual population or approximately how many, if any, persons might actually be exposed to the calculated value. The PECs determined from "what-if scenarios" may exceed PECs calculated based on realistic worst case scenarios.

Ambient Air Concentrations

Maximum annual average concentrations resulting from fugitive releases to air were predicted using the PMN PLUME Model (Versar, 1992a). This model is a computerized version of Turner's sector averaging form of the Gaussian algorithm (Turner, 1970). Concentrations were predicted for a receptor located at the facility fence line (assumed to be 100 meters down wind). Neutral atmospheric stability, an average wind speed of 5.5 m/sec, and wind direction toward the receptor 25% of the year were assumed. Because all of the release sources for a given facility were assumed to be within 100 meters of each other, all emissions were assessed as coming from a single representative stack assumed to be 3 meters in height.

The 1992 TRI data for all manufacturing sites indicates the following releases: 100 kg/yr (fugitive air release), 1390 kg/yr (stack releases), and 2825 kg/yr (off-site to waste water treatment); water releases, and on-site land releases were 0 kg/yr. TRI releases from processing and use operations in 1992 were 216000 kg/yr, with 2% released to air, 1% released to water, 53% released to land, and 44% released off-site (includes waste water treatment).

The PEC_{local} estimated from ambient air hydroquinone concentrations for the three manufacturing sites were negligible or 0 to 4.9×10^{-4} mg/m³ for fugitive emissions and 7.8×10^{-8} to 3.0×10^{-6} mg/m³ for stack emissions. The overall average air concentration was 8.2×10^{-5} mg/m³.

The PEC_{local} estimated from ambient air hydroquinone concentrations for processor and user sites were negligible or 0 to 8.5×10^{-3} mg/m³ for fugitive emissions and 0 to 8.1×10^{-6} mg/m³ for stack emissions. The highest average value for fugitive and stack emissions combined was 4.2×10^{-3} mg/m³.

Surface Water Concentrations

Surface water concentrations for the U.S.A. were calculated using site-specific receiving stream flow data obtained from Versar (1992a). Complete dilution of the chemical releases to the entire stream flow is assumed, but the effect of in stream degradation and removal processes was not addressed. For facilities which discharge waste water to a treatment plant (i.e., indirect dischargers), removal during waste water treatment was assumed to be 90% based primarily on expected biodegradation.

The PEC_{local} estimated as the harmonic mean surface water concentration for two manufacturing sites was negligible or zero and 8.2 $\mu\text{g/L}$ for a third site. For processors and users who were direct dischargers to fresh water, the harmonic mean surface water concentrations were estimated to be 8.2×10^{-5} to 6.8×10^{-2} $\mu\text{g/L}$ except for one discharge site which had an estimate of 180 $\mu\text{g/L}$. For processors who were indirect dischargers to fresh water, the harmonic mean surface water concentrations were estimated to be 1.9×10^{-5} to 0.88 $\mu\text{g/L}$ except for three discharge sites which were 1.3, 32, and 130 $\mu\text{g/L}$. For processors and users who were indirect discharges to salt water bodies, the estimated harmonic mean surface water concentrations were 1.5 $\mu\text{g/L}$ and 3.8 $\mu\text{g/L}$. The sea water discharge estimates refer to concentrations at the end of the discharge pipe without further dilutions, therefore, the values are overestimates of the actual environmental concentrations.

In 1977 and 1978 when discharges may have been greater than they currently are, U.S.E.P.A. contractors (Ewing *et al.*, 1977; Perry *et al.*, 1978) looked for but did not detect hydroquinone in surface waters associated with effluents from hydroquinone manufacturing sites.

Hydroquinone present in x-ray film developers can appear in the effluent from photoprocessors. Generic predicted environmental concentrations can be derived using the following scenarios (R. Diderich, personal communication), based on the EU-Technical Guidance Documents;

Scenario 1: It is supposed that the overflow (replenishment rate) of the processing solution is discharged into waste water by the photographic finishers (in this case mostly hospitals and medical practices).

Content of hydroquinone in fresh working strength solution:	5 - 25 g/L
Surface processed per day:	20 m^2/day (default)

The EU - Technical Guidance Document proposes to use a processed surface of 2000 m^2/d . This amount is valid for big photographic laboratories. For x-ray film, the highest consumption would be expected at large hospitals. According to the research institute INFU in Dortmund, Germany, a consumption of up to 6000 m^2/yr in mean sized hospitals (100 beds) and up to 20000 m^2/yr in large hospitals is to be expected. Even for a mean-sized hospital of 100 beds, it would not be appropriate to use the default waste water flow of 2000 m^3/d for the corresponding town (ca. 10000 inhabitants). It would be more realistic to place this hospital into a larger town of ca. 20000 inhabitants with a corresponding waste water flow of 4000 m^3/d . The processed surface would be 6000 m^2/yr (i.e., 20 m^2/d) for a release period of 300 d/yr).

Consumed processing solution:	350 ml/m^2 (default)
Percentage removed or converted during processing:	10%

Due to the high chemical reactivity of hydroquinone (autooxidation) a certain conversion can be assumed. No measured data are available though.

Waste water flow in the domestic waste water treatment plant:	4000 m^3/d (default)
Elimination in the waste water treatment plant:	91%
(SIMPLETREAT: log P_{ow} - 0.5, log H < 0, ready biodegradation)	
Dilution factor upon entering the surface water:	10 (default)

$$PEC_{local} = (0.005 * 350 * 20 * 0.9 * 0.09) / (4000 * 10) = 0.07 \text{ to } 0.35 \mu\text{g/l}$$

Scenario 2: It is supposed that the overflow is recycled. A part of the overflow, which is not fit for recycling is discharged. Additionally, part of the processing solution is discharged with the rinsing water into waste water (carry-over).

Percentage of processing solution not fit for recycling: 20% (default)
Carry-over rate: 0.1 L/m² (default)

$$PEC_{\text{local}} = (0.005 * (350 * 0.2 + 0.1) * 20 * 0.9 * 0.09) / (4000 * 10) = 0.014 \text{ to } 0.07 \text{ } \mu\text{g/L}$$

According to one formulator, the developing solution is not commonly recycled but rather the fixer solution is recycled. The above scenario is therefore probably not representative.

Scenario 3: It is supposed that the overflow is collected and not discharged into waste water. Only the carry-over is released into the waste water.

$$PEC_{\text{local}} = (0.005 * 0.1 * 20 * 0.09) / (4000 * 10) = 0.000023 \text{ to } 0.00011 \text{ } \mu\text{g/L}$$

Scenario 3 implies that the collected overflow is externally treated for silver recovery and that the spent solution is released to waste water after treatment. No scenario is available so far for the release during treatment of spent development solutions.

3.2 Effects on the Environment

3.2.1 Aquatic effects

The toxicity of hydroquinone to several species of fish, crustacea, and other organisms has been reviewed by IPCS (1994). The most significant results are listed in the attached SIDS Profile summary.

For the purposes of this assessment, a 96 hr LC₅₀ of 0.044 mg/L for *Pimephales promelas* was selected as the most sensitive fish toxicity value.

Kuhn *et al.* (1989) reported a calculated 48-hr LC₅₀ value (immobilization) of 0.29 mg/L for *Daphnia magna* in a test conducted according to DIN 38412, Part II. However for the purposes of this assessment, a 96 hr LC₅₀ = 0.05 mg/L for *Daphnia magna* was selected for analysis (Bringmann and Kuhn, 1977). Although this study was conducted before the 48-hr testing scheme became a standard length of exposure for this test, the LC₅₀ values of 0.12 mg/L for 24 hr and 0.05 mg/L for 96 hr provide reasonable estimates of toxicity for this species. Based on simple linear interpolation the 48 hr LC₅₀ is calculated to be 0.096 mg/L.

For the salt water shrimp, *Crangon septemspinosa*, the 84 hr LC₅₀ = 0.83 mg/L (McLeese *et al.*, 1979) was selected as a sensitive species for analysis.

A three-day EC₅₀ (growth) of 0.335 mg/L for *S. capricornutum* was selected as the most sensitive algal test for analysis.

Based on these data and calculations, hydroquinone is considered to have high acute toxicity for aquatic organisms.

The U.S.E.P.A. (1995a) has predicted ecotoxicity effect levels for a number of species. These values are shown along with experimentally determined values below.

Ecotoxicity Effect	Predicted Toxic Value (mg/L)	Experimental Value (mg/L)
Fathead Minnow LC ₅₀	0.060	0.044 (96 hr)
<i>Daphnia magna</i> LC ₅₀	< 1.0	0.050 (96 hr)
<i>C. septemspinosa</i> LC ₅₀	-	0.830 (84 hr)
<i>S. capricornutum</i> EC ₅₀	< 1.0	0.335 (72 hr)
<i>S. quadricauda</i> EC ₅₀		4 (96 hr) 0.93 (7 d)
Fish Chronic Value	< 0.100	
<i>Daphnid</i> Chronic Value	< 0.100	
Algal Chronic Value	< 0.100	0.600
Predicted values based on SARs for hydroquinones-quinones, MW = 110; LogPow = 0.81 (CLOGP); pH 7; hardness < 180.0 mg/L as CaCO ₃ ; TOC < 2.0 mg/L; solid; MP 169-171°C, Water Sol 73000 mg/l @25°C; hydrolysis t _{1/2} to quinone = 20 hr (U.S.E.P.A., 1995a).		

Estimation programs are based on mathematical relationships between Log P_{ow} and effect for a series of hydroquinones/quinones evaluated at the U.S. EPA. Acute toxicity coupled with persistence can produce long-term adverse effects in the environment. Due to the rapid degradation of hydroquinone by biotic and abiotic mechanisms, hydroquinone has not been labelled a long term hazard in a provisional classification for Europe.

3.2.2 Terrestrial Effects

Growth test on terrestrial plants OECD 208

Corn, Marigold, Lettuce, Radish

LOEC (corn) = 1000 mg/L
 NOEC (corn) = 100 mg/L
 LOEC = 100 mg/L
 NOEC = 10 mg/L

Seed germination test ASTM STP 1091

Ryegrass, Radish, Lettuce

LOEC = 100 mg/L
 NOEC = 10 mg/L

Significant exposure to the terrestrial environment is not expected. 1992 TRI data indicated no on-site land releases of hydroquinone from manufacturing sites. Of the 16000 to 66000 facilities estimated to process or use hydroquinone, only 5 reported releases to land which were on plant site. Since hydroquinone is a solid, which is unlikely to vaporize on spilling, spills to soil are expected to be easily recovered. Spills of hydroquinone-containing solutions (e.g., photographic developers) would also be insignificant sources of terrestrial contamination as the concentrates are supplied in small packages and the working solutions are typically dilute (0.5-2.5%).

3.2.3 Other effects

As hydroquinone readily biodegrades and photodegrades, it is unlikely to bioaccumulate. Hydroquinone largely partitions to the water compartments, therefore, effects in other compartments are not expected.

3.3 Initial Assessment for the Environment

3.3.1 Aquatic Compartment

The aquatic toxicity of hydroquinone to fresh water fish, *Daphnia*, and algae was between 0.050-0.335 mg/L; the predicted chronic values for these fresh water taxa were calculated to be < 0.100. The 84 hr LC₅₀ for the salt water shrimp, *C. septemspinosa*, was selected as the only salt water species for analysis. Based on these data and on the predicted aquatic toxicity values, the U.S.E.P.A. (1995a) identified concern concentrations or predicted no effect concentrations (PNECs) at 1.0 µg/L for fresh water species and 8.0 µg/L for salt water species.

Alternatively, a PNEC can be derived using the assessment factors recommended in the SIDS manual. As only acute effect data for fish and daphnids are available, an assessment factor of 100-1000 would be appropriate. Due to the large available database, a factor of 100 would be acceptable. Applied to the lowest experimental value of 0.044 mg/L (Fathead minnow), a PNEC of 0.44 µg/L can be derived.

These PNECs are compared to the maximum annual estimated water concentrations based on the 1992 TRI release levels and the "what-if scenarios" for manufacturing, processing, and use sites which were considered to be conservative estimates of the predicted environmental concentrations (PECs) (U.S.E.P.A., 1995).

For two of the manufacturing sites in the U.S.A., the surface water concentrations were predicted to be negligible or zero. Since both of these plants discharge to fresh water bodies the PEC/PNEC ratios are < 1. The third manufacturing plant discharges to a salt water body (Galveston Bay). In calculating the predicted surface water concentration critical dilution factors for this plant were not available and, therefore, the concentration predicted (8.2 µg/L) is the predicted concentration at the discharge point without mixing. When the PEC for salt water species (8.2 µg/L) is compared to the PNEC (8 µg/L) and the dilution of the discharge with sea water is considered, the PEC/PNEC ratio is < 1.

The estimated environmental surface water concentrations for processors and users have been separated into direct dischargers and indirect dischargers which discharge into publicly owned waste water treatment works.

All of the direct discharges are into bodies of fresh water. All but one of the direct discharge sites have PECs less than 0.07 µg/L and, therefore, the PEC/PNEC ratios range from 8.2×10^{-5} to 6.8×10^{-2} using a PNEC of 1.0 µg/L. One direct discharger has a predicted surface water concentration of 180 µg/L which would indicate a PEC/PNEC ratio of greater than one. However, in investigating site specific information for this discharger, it became apparent that the plant PEC/PNEC ratio was significantly less than 1 as no hydroquinone was detected from its NPDES-regulated outfall prior to discharge (O'Donoghue and David, 1995).

Among the indirect dischargers to fresh water there were three processor/users with estimated PECs above 1.0 µg/L. The PEC for these plants were reported to be 1.3, 32, and 130 µg/L. The PECs for all other plants in this category were less than 1.0 µg/L and had calculated PEC/PNEC ratios of 1.9×10^{-5} to 8.8×10^{-1} using a PNEC of 1 µg/L. The two processor/users with indirect discharges to the ocean had PECs of 1.5 µg/L and 3.8 µg/L. In both of these cases the critical dilution factors for these facilities were not available and, therefore, the predicted concentrations do not include a salt water dilution factor. The PEC/PNEC ratios for these plants prior to dilution are 0.19 and 0.48 using a PNEC of 1 µg/L.

Use of the alternative PNEC of 0.44 µg/L causes an additional four indirect discharges to exceed a PEC/PNEC ratio of one (PEC/PNEC ratios of 1.5-2.0), however, considering that there are estimated to be 16000 to 66000 processor/users of hydroquinone in the U.S.A., the number of predicted PEC/PNEC ratios ≥ 1 are small. Since all of the direct and indirect discharges identified in the exposure assessment have NPDES regulated discharges, it is very unlikely that they actually have discharges with PEC/PNEC ratios ≥ 1 . It is much more likely that the "what-if scenario" has overestimated the actual PEC.

Scenarios for the release of hydroquinone from photographic activities in Europe are estimated in Section 3.1.2. The PEC/PNEC ratios range from 5.2×10^{-5} - 7.9×10^{-1} using a PNEC of 0.44 µg/l.

The frequency of exceeding a PEC/NPEC of 1 can be calculated using the Probabilistic Dilution Model (PDM 3) program and the following inputs derived from the European exposure scenarios (R. Diderich, personal communication).

Days used/year:	300.
Concentration of HQ:	2.5% in highest working solutions = 0.025 g/ml.
Consumed processing solution:	350 ml/m ² .
Surface processed/day:	20 m ² .
Percent removal during processing:	10%.
Elimination in waste water treatment plant:	91%.

$$0.25 \text{ g/ml} \times 350 \text{ ml/m}^2 \times 20 \text{ m}^2/\text{d} \times 0.9 \times 0.09 = 0.014 \text{ kg/d}$$

Using this input to the PDM3 program, a concern concentration of 1 µg/L is predicted to be exceeded 0.5 days/yr (0.14% of the year) and a concern level of 0.044 µg/L is predicted to be exceeded 3 days/yr (0.81% of the year).

3.3.2 Terrestrial Compartment

Significant exposures to the terrestrial environment are not expected, therefore, an effects assessment was not conducted.

3.3.3 Other Compartments

Releases of hydroquinone to the air compartment are discussed in the human health section of this assessment.

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational Exposure

- Occupational exposure during hydroquinone manufacture.

Average concentrations in air during manufacturing and processing of hydroquinone have been reported to be in the range of 0.13 to 0.79 mg/m³ (IPCS, 1994). The average airborne hydroquinone concentration (~8000 breathing zone and area samples) in one hydroquinone manufacturing plant has decreased from 6.0 mg/m³ in the 1950's to 0.1 mg/m³ in 1990 (Pifer *et al.*, 1993).

Hydroquinone manufacture is a heavily automated procedure, thus only 81 employees in the U.S.A. are potentially exposed during manufacture, materials handling, maintenance, quality control sampling, and analysis. Employee protective clothing and engineering controls, such as local exhaust ventilation systems, are used to further prevent exposure at points in the process where exposure can occur.

"What-if scenarios" were used to estimate inhalation exposure levels in two U.S.A. manufacturing plants and calculated dose rates are shown in Table 2 (U.S.E.P.A., 1995). These estimated exposure levels assume that no personal protective devices are used. However, producers in the U.S.A. have reported the use of engineering controls (local exhaust and dust collectors) and personal protective devices (e.g., gloves, uniforms, goggles, respirators, boots) to control exposure, therefore, the calculated dose rates exceed actual expected dose rates.

Table 2
Estimated Occupational Inhalation Exposures Associated
with the Manufacture of Hydroquinone in the U.S.A.

Type of Worker	Number of Workers/Hours per Day/Days per Year	Airborne Concentrations ¹ (mg/m ³)		Potential Inhalation Dose Rate ^{2,3,4} (mg/kg/day)	
		Average	Maximum	Average	Maximum
Operator/Sampler	34/1->8/100-250	0.116	0.3	0.0166	0.0429
Loader/Packager	34/1->8/100->250	0.254	1.87	0.0363	0.267
Maintenance Personnel/Housekeeper	13/1-8/1-250	0.135	0.295	0.0193	0.0421

¹ Air concentrations are based on 29 samples.

² Assumes the medium work inhalation rate of 1.25 m³/hr (CEB, 1991).

³ Assumes the maximum number of hours in a range.

⁴ Assumes no use of PPE and that the chemical is 100% concentrated (CEB, 1991). Actual exposures may be less than estimated if PPE is properly selected, used, and maintained. Assumes 70 kg body weight.

Very rough bounding estimates of total dermal contact with hydroquinone (650-18200 mg/day) can be calculated using models which assume that employees regularly immerse their hands in hydroquinone for the entire work day without protective equipment (U.S.E.P.A., 1995; Versar, 1992 and 1992b). All U.S.A. manufacturers of hydroquinone report that engineering controls and personal protective equipment are used to minimize exposure, therefore, the bounding estimates significantly overestimate the potential contact that employees can have with hydroquinone dust.

As hydroquinone is a dry solid with a relatively high melting point (169°C), and because it is a polar substance and water soluble, it is unlikely that solid hydroquinone would be absorbed through the skin of manufacturing personnel. Even when dissolved in an aqueous medium, the absorption rate through human skin is expected to be slow and thus limit the amount absorbed (Barber *et al.*, 1995).

- Occupational exposure during processing and use

The number of employees working in U.S.A. industries which use hydroquinone has been estimated at 350000 to 560000 at 16000 to 66000 facilities (NIOSH, 1982-1984). The amount of exposure to hydroquinone in these work sites is not available and, therefore, for this analysis, it has been assumed that the exposures are equivalent to that of hydroquinone manufacturing employees (Table 2). There are several reasons to believe that this assumption will overestimate occupational exposures at processor/user sites. The first is that many operations which use or process hydroquinone are batch operations in which hydroquinone is added to hoppers, reactors, or mixing vessels which are then closed. In these types of operations, bags or drums are opened and their contents emptied out during periods of 10-60 min. Automation also reduces exposure to hydroquinone. For example, commercial photoprocessors are heavily automated and emissions from machines are typically below detectable levels (CMA, 1995). A study by the National

Institute of Occupational Safety and Health (NIOSH) did not detect hydroquinone in the atmosphere of rooms where film was being developed. Monitoring data are also available from the OSHA Compliance Information System on airborne concentrations of hydroquinone in processor/user facilities. The data base includes 78 air samples from facilities in 16 different standard industrial code categories. Seventy-seven of the samples were less than the analytical limit of detection or less than half of the PEL of 2 mg/m³; the majority of samples were below detectable levels.

Information from the United Kingdom indicates that there are 3000-5000 people estimated to be exposed to hydroquinone at work. The main route for work-related potential exposure is by inhalation (UKHSE, 1993).

In the manufacturing of photographic developers, monitoring data are commonly collected as total dust in the breathing zone or area samples. Estimates using this methodology overestimate actual exposure. Exposure levels recorded by manufacturers indicate the 8-hr TWA values are below 1 mg/m³ with average exposures at ~0.15 mg/m³ (UKHSE, 1993).

Measurements for hydroquinone among users of photographic developers indicate hydroquinone levels in the air below the analytical limit of detection (0.01 mg/m³; UKHSE, 1993).

Spills of photodevelopers in the workplace could result in exposure to hydroquinone. Actual exposure to hydroquinone in such circumstances would be expected to be minimal as hydroquinone has a low vapor pressure and a high vapor density which limit volatilization, and a slow penetration rate through the skin which limits absorption.

Biological monitoring of darkroom workers did not indicate an increase in work-related hydroquinone exposure as urinary hydroquinone levels were less than control worker values (UKHSE, 1993).

Estimates of employee exposures in other industries are shown in Table 3.

Table 3
Estimated Occupational Exposure Associated with the Processing of
Hydroquinone in the United Kingdom

Industry Category	Average Airborne Concentration ¹ (mg/m ³)	Potential Inhalation Dose Rate for Typical Exposure Periods ² (mg/kg)	
	Average (Maximum)	10 min	60 min
Food	0.42	1.2×10^{-3}	7.5×10^{-3}
Rubber	4.3 (10.2)	1.2×10^{-2} (2.9×10^{-2})	7.7×10^{-2} (1.8×10^{-1})
Agrochemical	0.03 (0.1)	8.6×10^{-5} (2.9×10^{-4})	5.4×10^{-4} (1.8×10^{-3})

- 1 Sampling periods were 5-120 min. Data obtained from UK manufacturers (UKHSE, 1993).
- 2 Assumes 1.25 m³ of air inhaled in 1 hr, 0.2 m³ of air inhaled in 10 min, 70 kg body weight, and that chemical hoppers or reaction vessels are filled once per 8-hr work shift. If vessels are loaded more or less frequently, the daily dose would differ accordingly.

The potential dose rates shown in Table 3 assume a worst case that personal protective equipment is not worn. Available information indicates that hydroquinone users in the UK rely on personal protective equipment for control of exposure. Current control measures in the UK maintain exposure levels below the TLV of 2 mg/m³ and in many cases below 1 mg/m³ (UKHSE, 1993). A combination of local ventilation and appropriate handling procedures should be adequate to control exposures below 0.5 mg/m³ 8-hr TWA (UKHSE, 1993).

4.1.2 Consumer Exposure

Photohobbyist exposure

Photohobbyists may be exposed to hydroquinone through dermal contact with developing solution or by inhalation of dry chemical used to prepare developing solutions.

Inhalation of hydroquinone dust by photohobbyists is expected to be negligible. Photohobbyists typically prepare developer solutions by pouring powdered developer into an appropriate volume of water. This process takes very little time (1-5 mins) and is not repeated until the developer solution is expended which might occur 1-4 times/month. Accidental spills of developer solution are likely to result in negligible inhalation exposures as hydroquinone has a low vapor pressure.

Although protective gloves or tongs are recommended when handling hydroquinone-containing black-and-white developers, dermal exposure may occur as a result of a spill or splash on unprotected skin areas. Actual absorption of hydroquinone through the skin, however, can be expected to be negligible to minimal for several reasons. First, black-and-white developers typically contain only 0.5-2.5% hydroquinone limiting the exposure concentration. In addition, hydroquinone is only slowly absorbed through the skin. The flux (i.e., the amount of chemical absorbed across a defined surface area of the skin per unit time) for hydroquinone from an aqueous solution formulated to represent a developing solution is approximately 0.5 mg/cm²/hr (Barber *et al.*, 1995). Barber *et al.* (1995) estimated the amount of hydroquinone absorbed through the skin if an individual immersed one hand in a 5% hydroquinone developer for 1 hr to be 200 µg or 2.9×10^{-3}

mg/kg for a 70 kg person. Actual absorbed doses of hydroquinone can be expected to be much lower. If recommended practices are not followed, the surface area of the skin exposed to hydroquinone by putting a hand into a developer tray is small as developer trays are typically 5-10 cm in depth and photographs would be grasped by their edge. Thus, a typical unprotected exposure would involve the tips of three fingers of one hand. The exposure time to hydroquinone would also be brief as a photohobbyist not using tongs or gloves would be expected to carry this habit forward and dilute any hydroquinone on the hands with stop bath, wash water, and fixer. Alternatively, if the photohobbyist intended to reduce contamination of post-developer solutions with developer, the photohobbyist would have to wipe his/her hands between trays resulting in removal of hydroquinone by toweling and dilution.

Biological monitoring of professional darkroom workers in the U.K. revealed no increase in urinary excretion of hydroquinone (UKHSE, 1993), thus exposure of photohobbyists, who can be expected to spend considerably less time exposed to hydroquinone, is expected to be negligible.

Cosmetic, non-prescription drug, and prescription drug exposure

Dermal exposure may also result from the use of cosmetic or medical products containing hydroquinone, such as skin lighteners. The E.U. countries have restricted its use in cosmetics to 2% or less. In the U.S.A., the Food and Drug Administration restricts hydroquinone concentration to 1.5 - 2% in non-prescription skin lighteners. Concentrations up to 4% may be found in prescription skin lighteners.

Cosmetic exposure to hydroquinone is limited to few products. In 1984, FDA product formulation information indicated that hydroquinone was present at concentrations of $\leq 1\%$ in 185 out of 1112 hair dye and coloring products (CIR, 1994). It was also present in 21 out of 2031 other skin care preparations at 1-5% (CIR, 1994). In hair dyes, hydroquinone acts as a regulating agent and is consumed during the dyeing procedure (CIR, 1994). Simulated dyeing procedures demonstrated that within 4 mins, 50% of the hydroquinone is already consumed while after 30 min $< 3\%$ of the initial amount remained (CIR, 1994).

As the actual concentration of hydroquinone decreases sharply as the color-forming reaction occurs, the amount of hydroquinone absorbed is limited both by decreasing concentration and the length of time the hair dye is applied before being rinsed off (CIR, 1994). The CIR (1994) concluded that hydroquinone is safe at concentrations of $\leq 1.0\%$ for aqueous cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair. The CIR also stated that hydroquinone should not be used in leave-on non-drug cosmetic products.

Hydroquinone is also used in products intended to lighten small areas of skin. 2% Hydroquinone preparations are the only agents considered safe and effective for over-the-counter treatment of cutaneous hyperpigmentation (Fed. Reg., 1978 and 1982). This type of use has sometimes been incorrectly referred to as "skin bleaching," however, hydroquinone does not bleach the skin. Instead, it is thought to act through competitive inhibition of tyrosinase resulting in a gradual fading of hyperpigmented spots by a reduction in the formation of new pigment. Skin lighteners, which are regulated in the E.U. and the U.S.A. (Food and Drug Administration), are undergoing reviews.

New labeling guidelines for skin lightening products were put into place in May 1992 by the Non-Prescription Drug Manufacturers. Key aspects of the new guidelines include: apply a small amount of lightener as a thin layer to the affected areas of dark brownish skin discoloration; use with a sunscreen to prevent or minimize reoccurrence of pigmentation; discontinue use after the discoloration is gone; apply again only if the discoloration reappears, stop use if any skin irritation becomes severe or any darkening persists; do not use with other topical products containing

resorcinol, phenol, or salicylic acid; do not apply to inflamed or broken skin; and test overnight on a small section of skin inside the elbow for sensitivity.

Misuse of products containing higher concentrations of hydroquinone and products containing phenol, resorcinol, salicylic acid, and mercury in addition to hydroquinone led to restrictions on skin lighteners in South Africa to 2% hydroquinone.

4.1.3 Indirect Exposure Via the Environment

Estimates of predicted environmental concentrations (PEC) from hydroquinone manufacturing, processing, and use are based on 1992 TRI data reported to the U.S.E.P.A. (1995). These "what-if scenarios" estimates of hydroquinone concentration in air and water were made using simple, conservative atmospheric dispersion models (EAB, 1994; Versar, 1992a). The "what-if scenarios" have been developed to assess potential exposure under a set of hypothetical conditions or under a set of conditions for which actual exposure parameter data are incomplete or non-existent. The calculated PECs are not intended to provide information about how likely the combination of exposure parameter values might be in the actual population or approximately how many, if any, persons might actually be subjected to the calculated value. The PECs determined from "what-if scenarios" may exceed PECs calculated based on realistic worst case scenarios.

Maximum annual average concentrations resulting from fugitive releases to air were predicted using the PMN PLUME Model (Versar, 1992a). This model is a computerized version of Turner's sector averaging form of the Gaussian algorithm (Turner, 1970). Concentrations were predicted for a receptor located at the facility fence line (assumed to be 100 meters down wind). Neutral atmospheric stability, an average wind speed of 5.5 m/sec, and wind direction toward the receptor 25% of the year were assumed. Because all of the release sources for a given facility were assumed to be within 100 meters of each other, all emissions were assessed as coming from a single representative stack assumed to be 3 meters in height.

The estimated ambient hydroquinone air concentrations from three manufacturing sites were 0 to 4.9×10^{-4} mg/m³ for fugitive emissions and 7.8×10^{-8} to 3.0×10^{-6} mg/m³ for stack emissions. The estimated general population inhalation exposure from fugitive emissions were negligible for two sites and 4.3 or 1.7×10^{-4} mg/kg/day for the third site. The estimated exposures for stack emissions were 7.8×10^{-4} to 1.1×10^{-2} mg/person/year or 3.1×10^{-8} to 4.3×10^{-7} mg/kg/day. Estimated exposure due to drinking water and fish ingestion were negligible at all manufacturing sites.

The estimated ambient hydroquinone air concentrations for fugitive emissions from 29 processor/user sites were zero or negligible to 24 mg/person/day or 0 to 9.4×10^{-4} mg/kg/day (U.S.E.P.A., 1995). The estimated ambient hydroquinone air concentrations of stack emissions were 0 or negligible to 8.1×10^{-2} mg/person/yr or 0 to 3.2×10^{-4} mg/kg/day. The average estimated ambient hydroquinone air concentration from 29 processor/user sites reported in the 1992 TRI data base for fugitive emissions was 29.4 mg/person/year and for stack emissions was 6.7×10^{-3} mg/person/yr (U.S.E.P.A., 1995) or 1.1×10^{-3} to 0.26×10^{-7} mg/kg/day.

The estimated exposures resulting from direct surface water discharges of hydroquinone were 4.1×10^{-5} to 3.4×10^{-2} mg/person/yr or 1.6×10^{-9} to 1.3×10^{-6} mg/kg/day for four processor/user sites (U.S.E.P.A., 1995). A fifth site was not included in the estimates because the TRI data did not reflect actual discharge estimates (CMA, 1995). The average estimated exposure resulting from direct surface water discharges at four processor/user sites is 1.5×10^{-3} mg/person/yr or 5×10^{-7} mg/kg/day (U.S.E.P.A., 1995).

The estimated exposures resulting for indirect surface water discharges of hydroquinone at processor/user sites were 9.3×10^{-6} to 67 mg/person/yr or 3.6×10^{-10} to 2.6×10^{-3} mg/kg/day (U.S.E.P.A., 1995). The average estimated exposure resulting from indirect surface water discharges at 16 processor/user sites (U.S.E.P.A., 1995) was 5.4 mg/person/yr or 2.1×10^{-4} mg/kg/day.

Hydroquinone exposure through drinking water and fish consumption were considered negligible for processor/user sites (U.S.E.P.A., 1995).

4.2 Health Effects Data

4.2.1 Mode of action, toxicokinetics, and metabolism

Hydroquinone is rapidly and extensively absorbed from the gut and lungs of animals. Absorption via the skin is slow but may be accelerated with vehicles such as alcohols. Hydroquinone distributes rapidly and widely among tissues. It is metabolized to 1,4-benzoquinone and other oxidized products, and is detoxified by conjugation to monoglucuronide, monosulfate, and mercapturic derivatives. The excretion of hydroquinone and its metabolites is rapid, and occurs primarily via the urine.

Covalent binding and oxidative stress are mechanisms postulated to be associated with hydroquinone-induced toxicity (IPCS, 1994). Oxidized hydroquinone metabolites may covalently bind cellular macromolecules or alkylate low molecular weight nucleophiles (e.g., glutathione (GSH)) resulting in enzyme inhibition, alterations in nucleic acids and oxidative stress; however, redox cycling is not likely to contribute significantly to oxidative stress (IPCS, 1994). The reaction of hydroquinone metabolites with GSH results in the formation of conjugates which can be further processed to cysteine conjugates which are postulated to cause kidney toxicity (IPCS, 1994, Whysner *et al.*; 1995; English *et al.*, 1994). Cell proliferation associated nephrotoxicity in a sensitive strain and species of animal (male F344 rat) has been postulated to be involved in the production of renal tumors in rats (Whysner *et al.*, 1995; English *et al.*, 1994 and 1994a).

4.2.2 Interaction with Phenols:

Recently there have been a number of studies reporting interactive effects between hydroquinone and other phenolic compounds (IPCS, 1994). Initially, Eastmond *et al.* (1987) showed that the co-administration of hydroquinone and phenol (75 mg/kg), when given by intraperitoneal injection twice per day, produced a synergistic decrease in bone marrow cellularity in B6C3F₁ mice that was similar to that induced by benzene. This compound treatment was significantly more myelotoxic than that observed when either hydroquinone or phenol was administered separately. Associated *in vitro* studies suggested that this interactive effect was due to a phenol-induced stimulation of the myeloperoxidase-mediated conversion of hydroquinone to 1,4-benzoquinone in the bone marrow. Subsequent studies have indicated that interactions between hydroquinone and other phenolic compounds can result in a variety of cytotoxic, immunotoxic and genotoxic effects. Studies conducted using routes of exposure relevant to risk assessment in occupational or environmental situations have not been conducted.

4.2.3 Non-Human Data

a) Acute toxicity

Oral: OECD 401

Rat (?)	LD ₅₀ = 390 mg/kg
Rat (Osborne-Mendel)	LD ₅₀ = 302 mg/kg
Rat (Wistar)	LD ₅₀ = 298 mg/kg
Rat (Sprague)	LD ₅₀ = 323 mg/kg
Mouse (?)	LD ₅₀ = 680 mg/kg
Mouse (Swiss)	LD ₅₀ = 390 mg/kg

Dermal: OECD 402

Guinea pig (?)	LD ₅₀ = > 1000 mg/kg
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Sensitization: OECD 406

Magnussen-Kligman:	sensitizer
Draize:	weak sensitizer

Hydroquinone exhibits moderate acute oral toxicity for animals. The IPCS reported that limited data suggest that powdered hydroquinone causes transient eye irritation and corneal opacity in dogs and guinea-pigs; in rabbits powdered hydroquinone induced slight irritation of the eye. Hydroquinone may be a skin sensitizer in animals. The ability to induce sensitization has been found to vary from "weak" to "strong" depending on the test procedure and vehicle used.

b) Repeated dose oral toxicity

Rat (Sprague-Dawley)	NOEL (oral) = 20 mg/kg (13 w)
Rat (F-344)	NOEL (dermal) = 1920 mg/kg (14 d)
Mouse (B6C3F ₁)	NOEL (dermal) = 4800 mg/kg (14 d)
Rat (F-344)	NOEL (oral) < 25 mg/kg (13 w)
Mouse (B6C3F ₁)	NOEL (oral) < 25 mg/kg (13 w)
Rat (F-344)	NOAEL (dermal) = 74 mg/kg (13 w)

Repeated oral dosing caused tremors and reduced activity (≥ 64 mg/kg), reduced body weight gain (≥ 200 mg/kg), convulsions (≥ 400 mg/kg), and nephropathy in F-344 rats (≥ 100 mg/kg). No adverse effects on the kidneys were reported in Sprague-Dawley rats treated for the same length of time with the same dose levels. Effects in mice include tremors and convulsions (400 mg/kg), increased liver weight (≥ 25 mg/kg), and irritation of the forestomach (≥ 200 mg/kg). A functional-observational battery and neuropathological examinations of rats failed to give any evidence of persistent or structural neurotoxicity after repeated dosing for 90 days. A NOEL for all effects was 20 mg/kg per day.

c) Repeated dose dermal toxicity

Fourteen days of repeated dermal dosing caused reduced body weights of male rats at the 3840 mg/kg dose level (6% relative to the controls), but the body weights of female rats at this dose level and of mice at 4800 mg/kg were comparable to controls. There were no clinical signs of toxicity in either species. Prolonged dermal dosing over 13 weeks with 2.0, 3.5, or 5.0% hydroquinone in an oil-in-water emulsion cream resulted in minimal to minor dermal irritation, but no overt toxicity. No adverse effects or compound-related effects occurred in organ weight, clinical pathology, or histopathology. A NOEL was not determined because of the dermal irritation in all treated groups,

but the NOAEL was the highest dose level of 5% hydroquinone (74 mg/kg in males and 110 mg/kg in females) based on the lack of systemic effects.

d) Reproductive toxicity

Rat (Sprague-Dawley)	NOEL = 15 mg/kg (General toxicity)
	NOEL = 150 mg/kg (Repro. Tox. parental)
	NOEL = 150 mg/kg (Repro. Tox. F ₁)

A two-generation reproduction study was conducted in rats. The NOAEL for reproductive effects through two generations was 150 mg/kg per day (the highest dose tested).

e) Genetic toxicity

Bacterial (Ames) test:	not mutagenic with or without activation
<i>In vitro</i> chromosomal aberration test:	positive with activation, negative without activation
<i>In vivo</i> micronucleus test:	positive by ip injection, weak by oral gavage
Dominant lethal assay:	negative
Mouse spot test:	negative

Numerous genotoxicity studies of hydroquinone have been conducted. Hydroquinone is not mutagenic in the *Salmonella*/microsome test. Other data indicate that hydroquinone induces structural chromosome aberrations and c-mitotic effects *in vivo* in mouse bone-marrow cells following ip injection. *In vitro* studies with various cell lines showed that hydroquinone was capable of inducing gene mutations, structural chromosome aberrations, sister-chromatid exchange, and DNA damage. Hydroquinone produces adducts with DNA *in vitro*, but recent *in vivo* studies were unable to produce DNA adducts. While several experiments with hydroquinone have shown mutagenic effects; the relevance of these results to human risk is uncertain (IPCS, 1994). The majority of positive mutagenicity studies use routes of exposure (parenteral or *in vitro*) which are not relevant to human exposures. A dominant lethal assay in rats was negative.

f) Other health related information

Carcinogenicity:

Rat (Sprague-Dawley)	negative at 1.0% in diet
Rat (F-344)	renal tubular adenomas in male rats and mononuclear cell leukemia in female rats at 25 and 50 mg/kg
Mouse (B6C3F ₁)	hepatocellular adenomas in female mice at 50 and 100 mg/kg; hepatocellular adenomas in male mice at 1046 mg/kg

A study by Carlson and Brewer (1953) using Sprague-Dawley rats treated for two-years with hydroquinone in the diet indicated "atrophy of the liver cord cells, lymphoid tissue of the spleen, adipose tissue, and striated muscle together with superficial ulceration and hemorrhage of the stomach mucosa" but no carcinogenesis. Two-year studies performed by the NTP reported that

hydroquinone exposure was associated with some evidence of carcinogenicity in F-344 rats and B6C3F₁ mice. In the NTP study, renal tubular cell adenomas occurred in male rats and mononuclear cell leukemia in female rats, and hepatocellular neoplasms, mainly adenomas, in female mice. The NTP concluded that these data indicated "some evidence of carcinogenic activity" in male and female rats and in female mice. In a study by Shibata *et al.* (1991) using F-344 rats and B6C3F₁ mice, renal tubular cell adenomas were also noted in male rats; hepatocellular adenomas and renal cell hyperplasia were noted in male mice; and hyperplasia of the forestomach was noted in both male and female mice fed 0.8% hydroquinone diets for two years. The evidence provided by cancer bioassay studies is considered limited (IPCS, 1994). A U.S.E.P.A. (1990) review of the NTP bioassay found the bioassay results provide limited evidence of carcinogenicity in animals.

Studies by English *et al.* (1994) of cell proliferation in the kidneys of F-344 and Sprague-Dawley rats indicate that a dose level of 50 mg/kg hydroquinone resulted in cell proliferation in the kidney and excretion of urinary enzymes indicative of proximal tubule damage but only in male F-344 rats. Female F-344 rats and male Sprague-Dawley rats were unaffected. Thus, renal carcinogenicity may be limited to male F-344 rats via a mechanism including nephrotoxicity and increased cell proliferation.

g) Developmental toxicity

Rat (Sprague-Dawley)	NOEL = 100 mg/kg (General toxicity) NOEL = 300 mg/kg (Pregnancy/litter) NOEL = 300 mg/kg (Fetal data)
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Rabbit (NZW)	NOEL = 25 mg/kg (General toxicity) NOEL = 75 mg/kg (Pregnancy/litter) NOEL = 75 mg/kg (Fetal data)
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Oral dosing of pregnant rats on days 6-15 of gestation with 100 or 300 mg/kg caused maternal toxicity at the higher dose level (a statistically significant reduction in body weight gain and feed consumption). A reduction in mean fetal body weight was correlated with the reduced maternal body weight. No compound-related teratogenic effects were produced at this dose level; thus, 100 mg/kg was considered the NOEL for maternal and developmental toxicity in rats. Findings of increased resorption rates in rats given hydroquinone orally at about 100 mg/kg per day were not confirmed in this study, and, consequently, the NOAEL for maternal reproductive effects and teratogenicity was 300 mg/kg. In rabbits, 150 mg/kg caused reductions in body weight and feed intake and an increased (but not statistically significant) incidence of malformations in the fetuses. The malformations may have been associated with maternal toxicity. The dose level of 200 mg/kg produced an increased number of resorptions, indicating embryotoxicity. The NOEL for developmental toxicity in rabbits was 75 mg/kg per day.

h) Dermal Absorption

The rate of percutaneous absorption of a 5% aqueous hydroquinone solution through human stratum corneum and whole rat skin was measured *in vitro* (Barber *et al.*, 1995). The absorption rate through human skin is 0.522 µg/cm²/hr. The absorption rate through rat skin is 1.09 µg/cm²/hr. This absorption rate is considered to be "slow" based on published definitions of absorption (Marzulli *et al.*, 1969).

4.3 Initial Assessment for Human Health

4.3.1 Occupational Exposure

- Health Assessment for Hydroquinone Manufacture

The primary route of exposure to hydroquinone during its manufacture is the inhalation route. The highest average estimated inhalation dose of hydroquinone during manufacturing is 0.0363 mg/kg/day for loader packagers (Table 2). The highest estimated maximum inhalation dose of hydroquinone is 0.267 mg/kg/day. Inhalation studies with experimental animals are not available for comparison to these estimates, however, comparison to the most sensitive oral dose NOEL (15 mg/kg/day) observed in the rat reproduction study provides a worst case Estimated Human Exposure/Estimated Dose of Low Concern (EHE/EDLC) ratios of 2×10^{-3} (highest average exposure group) and 1.8×10^{-2} (highest maximum exposure group).

EHE/EDLC ratios for all other manufacturing employees would be expected to be smaller.

Dermal absorption of hydroquinone by manufacturing employees is estimated to be negligible for several reasons: manufacturing is conducted in closed systems, all manufacturers report use of personal protective equipment, manufacture involves exposure to only dry crystalline solid material, and the physical properties of hydroquinone (relatively high melting point, polar substance, water solubility) limit the potential for absorption. No published reports of dermal toxicity or sensitization have been reported to be associated with hydroquinone manufacturing.

Ocular lesions of varying degree have been described in employees of a U.S.A. plant manufacturing hydroquinone (Anderson, 1947 and 1958; Oglesby *et al.*, 1947; Sterner *et al.*, 1947). Concomitant exposure to 1,4-benzoquinone was reported in the plant and the corneal damage observed may have been associated with oxidation products of hydroquinone rather than the parent material. The airborne concentrations of hydroquinone and quinone present at the time ocular damage was seen were much higher than the current TLV of 2 mg/m³. The corneal damage observed occurred gradually over several years of exposure and no serious cases were seen until after 5 or more years of exposure (IPCS, 1994).

Following recognition in 1947 of the possibility that hydroquinone manufacturing practices could be associated with serious ocular damage, control measures were put into place and regular air monitoring and ocular examinations were conducted. Based on the experience gained during monitoring activities an exposure value of 0.1 ppm quinone vapor and 2-3 mg/m³ hydroquinone dust (time-weighted average) were recommended to control eye irritation which was considered a prelude to the onset of ocular pigmentation. The lower recommended value for hydroquinone (2 mg/m³) was eventually adopted as the ACGIH 8-hr time-weighted TLV value. Experience with this TLV in U.S.A. hydroquinone manufacturing plants has demonstrated its utility in controlling occupational exposures for ocular damage. Since no animal model has been developed for the ocular effects observed during hydroquinone manufacturing, it is difficult to know the size of the EHE/EDLC ratio. However, it is possible to calculate a TLV/current exposure ratio which spans the range of 5.8×10^{-2} to 1.27×10^{-1} for loader/packer and operator/sampler employee exposures.

Calculation of an EHE/EDLC or other quantitative endpoint for carcinogenicity is not considered appropriate for this analysis because of the limited evidence of carcinogenicity provided by animal studies. This view is supported by statements published by the U.S.E.P.A. in relationship to methodologies for analysis of animal bioassay when the animal data cannot be interpreted to indicate clear evidence of carcinogenicity.

Both IPCS (1994) and the U.S.E.P.A. (1990) have found the animal bioassay data for hydroquinone to provide limited evidence of carcinogenicity in animals. Since these reviews have been completed, additional mechanistic data have been collected which indicate that the primary tumor of concern, kidney adenomas in male rats, may be associated with cell proliferation brought about by chronic renal toxicity and age-induced nephropathy in an unusually sensitive strain and sex of animal (male F344 rats).

In addition, a recently completed epidemiology study of hydroquinone manufacturing employees reduces concern levels for carcinogenicity further (Pifer, 1995). Mortality in a 1942-1990 cohort of 858 men and 21 women employed in the manufacture and use of hydroquinone was evaluated through 1991. The population studied included all hydroquinone manufacturing and use personnel for a 50 yr period for the largest U.S.A. producer of hydroquinone. Average exposure concentrations, 1949-1990, ranged from 0.1 to 6.0 mg/m³ for hydroquinone dust and from less than 0.1 to 0.3 for quinone vapor (estimated 8-h time-weighted averages). Compared with general population and occupational referents there were statistically significant deficits in total mortality and deaths due to cancer. No significant excesses were observed for such hypothesized causes as kidney cancer [2 observed vs. 1.3 expected (both control groups), $p \sim 0.39$], liver cancer (0 vs. 0.8, 1.3), and leukemia (0 vs. 2.3, 2.7). Dose-response analyses of selected causes of death, including renal carcinoma, demonstrated no statistically significant heterogeneities or linear trends according to estimated career hydroquinone exposure (mg/m³-years) or time from first exposure.

In 1992, this same plant employed 76 of 81 or 93.8% of the U.S.A. manufacturing employee population for hydroquinone. Based on 1992 production volumes, this plant is estimated to employ half of all hydroquinone production employees in the world. Considering the limited nature of the animal bioassay data and the absence of evidence of carcinogenicity in a large fraction of the hydroquinone manufacturing employees, the current control measures in place are considered adequate for protecting human health.

- Health Assessment for Hydroquinone Processing and Use

The inhalation route is considered to represent the main route of exposure for employee exposures in industries processing or using hydroquinone. In industries which make photographic developers containing hydroquinone and in those which use hydroquinone developers average exposure concentrations (UKHSE, 1993) are ~ 0.15 mg/m³ (developer manufacturers) and < 0.01 mg/m³ (developer users). Estimated doses for these exposures are $\sim 2.1 \times 10^{-2}$ mg/kg/day (developer manufacturers) and $< 1.4 \times 10^{-3}$ mg/kg/day (developer users). When compared to the most sensitive oral dose NOEL (15 mg/kg/day) observed in the rat reproduction study, EHE/EDLC ratios are 1.4×10^{-3} (developer manufacturers) and $< 6.7 \times 10^{-4}$ (developer users).

For other processor/user employee groups (Table 3), the highest average inhalation dose rate is estimated to be 7.6×10^{-2} mg/kg/day. The EHE/EDLC ratio for this exposure is 5.1×10^{-3} assuming the longest exposure is 1 hr/day. If instead it is assumed that the maximum reported average airborne concentration were continued for 8-hr, the EHE/EDLC would still not be ≥ 1 .

Dermally absorbed doses of hydroquinone dust are estimated to be negligible for the same reasons considered relevant for manufacturing employees.

A small number of case reports involving dermal sensitization or depigmentation have been reported among employees of processors or users of hydroquinone containing developers. These include two case reports of vitiligo-like depigmentation. One case (Frenk and Loi-Zedda, 1980) involved a black man who frequently immersed his right arm and forearm in 0.06% hydroquinone

developer. Irregular depigmented spots developed on the arm and forearm after 8-9 months. The second case report involved a black man who showed signs of focal depigmentation on the hands, wrists, and mouth, however, exposure to hydroquinone was not confirmed. The man worked servicing automatic self-photography machines which used a 7% hydroquinone developer solution (Kersey and Stevenson, 1981).

Lidén (1984) during an investigation of occupational dermatoses in a movie film laboratory, patch tested 23 employees and 200 controls with 1% hydroquinone in petrolatum. None of the individuals had positive test results. Lidén (1989) re-examined this same facility after improvements had been made to the facility and occupational dermatoses had been reduced. The population patch-tested included individuals with chemical exposures or occupational dermatosis from a plant population of 78 employees. Of seven individuals tested with aqueous or petrolatum mixtures of up to 1% hydroquinone, four had positive reactions of unstated severity. Three of the four individuals, however, did not demonstrate evidence of an occupational dermatosis. One woman who tested positive did have hand eczema. This woman also had reactions to other chemicals in the work environment and had apparently tested negative to hydroquinone in the earlier study (Lidén, 1984) when she also had signs or symptoms of eczema as no new cases were reported in this facility following modernization. Thus, although the report describes 4 of 7 people with positive skin reactions, 3 cases were asymptomatic and one may have been exacerbated but not induced by hydroquinone.

The ocular lesions observed for hydroquinone manufacturing employees either do not occur in processing/user employees or occur with a very low frequency as published reports for processor/user populations are not available. The most likely reasons for this difference is that exposures to hydroquinone are lower, exposure durations are shorter, and exposure periods are less frequent.

Current experience with handling hydroquinone indicate that measures in place are adequate to control occupational dermal reactions to hydroquinone.

As indicated in the section assessing carcinogenicity for hydroquinone manufacturing employees, animal data on carcinogenicity are considered limited. As exposures in processor/user employee populations are estimated to be lower than for manufacturing employees, the risks associated with processing and use activities should also be lower. Epidemiologic evidence supports the conclusion that measures in place are adequate to control risks associated with hydroquinone.

4.3.2 Health Assessment for Consumer Exposure

- Health Assessment for Photohobbyist Exposure

Photohobbyist health risks associated with inhalation of hydroquinone are estimated to be negligible as exposure potential is estimated to be well below that of occupational groups.

If it is assumed that a photohobbyist immerses his/her hand in a 5% hydroquinone photodeveloper for 1 hr/day, the absorbed hydroquinone dose would be 2.9×10^{-3} mg/kg/day. When this value is compared to the most sensitive oral dose NOEL (15 mg/kg/day) observed in the rat reproduction study the EHE/EDLC ratio is 1.9×10^{-3} .

Cases of ocular damage and depigmentation which have been reported in occupationally exposed groups have not been reported for photohobbyists and thus if such endpoints do occur, they occur at

very low incidences. Based on the low potential for exposure and the absence of reported adverse effects, measures in place to control health risks are considered to be adequate.

- Health Assessment for Cosmetic, Non-Prescription Drug, and Prescription Drug Exposures

The Cosmetic Ingredient Review (CIR) recently extensively reviewed the use of hydroquinone in cosmetic formulations in the U.S.A. Based on its review, the CIR (1994) found that hydroquinone as used in hair coloring preparations is a consumable and therefore exposure to hydroquinone is limited. The CIR concluded that hydroquinone is safe at concentrations of $\leq 1.0\%$ for aqueous cosmetic formulations designed for discontinuous, brief use following rinsing from the skin and hair and that it should not be used in leave-on non-drug cosmetic products. A review of hydroquinone use in cosmetics is currently underway in the EU.

The use of 2% hydroquinone in skin lightening products to control hyperpigmentation has been considered safe and effective by the U.S.F.D.A. (Fed. Reg. 1978 and 1982). At the present time, the use of hydroquinone in skin lighteners is being reviewed both in the U.S.A. and the EU. A recent survey of the literature for cases of adverse outcomes (exogenous ochronosis) from use of 2% hydroquinone creams found only 17 cases in the U.S.A. (Burke and Maibach, 1997). A survey conducted by the Non-Prescription Drug Manufacturers covering responses from 2108 American physicians with a collective patient population of 44 million yielded 46 cases of exogenous ochronosis. The American experience with skin lighteners is different from that reported in South Africa where until 1984 the amount of hydroquinone in skin lighteners was not controlled and adverse reactions were commonly reported. The South African experience differs from the American experience in a number of ways since the South African skin lighteners also contained phenol and resorcinol.

Hardwick *et al.* (1989) has reported a high incidence of ochronosis among black persons in the U.K. associated with the use of 2% hydroquinone creams. The reasons for the difference between the American and British experience with skin lighteners is not clear but it may depend on a difference in use patterns as the example of a use pattern shown in a brief note by Godlee (1992) differs from the recommended method of use in the U.S.A.

A small number of cases of other types of adverse effects (leukoderma and brown staining of the finger nails) have been reported among users of hydroquinone (Mann and Harman, 1983; Pray, 1993; IPCS, 1994). Dermal sensitization associated with use of skin lighteners is considered negligible (Pray, 1993).

As voluntary changes have been made to the labelling of product and the use of skin lightener creams is under review in the U.S.A. and EU, current activities to control hazards associated with the use of hydroquinone in skin lighteners are considered adequate.

Published or unpublished reports associated with adverse reactions to prescription use of hydroquinone are rare. A single case of dermal cross-sensitization in a patient exposed to both 2% hydroquinone and 5% hydroquinone monobenzyl ether is described (IPCS, 1994).

- Health Assessments for Other Exposures to Hydroquinone

Two reports have been published on possible skin sensitization reactions to hydroquinone from use of rubber footwear in Brazil and India (George *et al.*, 1990; Moriearty *et al.*, 1978). These reports appear to be isolated events which cannot clearly be linked to hydroquinone exposure.

A small number of poisoning or suicides have been attempted with hydroquinone or hydroquinone-containing developers. Individuals have survived estimated doses of 1g and 12g hydroquinone. The last hydroquinone poisoning was reported in 1927. A small number of deaths have been reported following ingestion (accidental or suicidal) of hydroquinone containing developers. Reports of these cases occurred in 1939, 1945, 1969, and 1974 (IPCS, 1994). The current classification of "harmful if ingested" is considered adequate to control such unintended exposures.

- Health Assessment for Indirect Exposure via the Environment

Using the most sensitive oral dose NOEL observed in the rat reproduction study (15 mg/kg/day), EHE/EDLC ratios can be estimated for ambient air and water exposures at manufacturing and processor/user sites (U.S.E.P.A., 1995).

The EHE/EDLC ratios for fugitive air emissions at manufacturing sites were 0 for two sites and 1.1×10^{-5} for the third site. The EHE/EDLC ratios for stack air emissions were 2.1×10^{-9} to 2.9×10^{-8} . The EHC/EDLC ratios for surface water, drinking water, and fish consumption were all considered negligible.

The EHE/EDLC ratios for fugitive air emissions at processor/user sites were 0 to 6.3×10^{-5} . The EHE/EDLC ratios for stack emissions were 0 to 1.3×10^{-8} . The EHC/EDLC ratios for direct surface water discharges were 1.1×10^{-10} to 8.7×10^{-8} . The EHC/EDLC ratios for indirect surface water discharges were 2.4×10^{-11} to 1.7×10^{-4} . The EHC/EDLC ratios for drinking water and fish consumption were all considered negligible for processor/user sites.

As all ambient environmental exposures are estimated to be considerably less than occupational exposures, carcinogenicity concerns are considered negligible. The U.S.E.P.A. (1990) assessed potential for adverse health based on the 1987 TRI database for hydroquinone (201470 kg/yr total TRI reported release as compared to the 1992 total TRI release of 4315 kg/yr). The 1990 U.S.E.P.A. analysis also concluded ambient air and water releases resulted in negligible health risks. Since the 1992 total TRI release was only 2% of the 1987 TRI release, any potential risk should be equivalently lower.

The low EHE/EDLC ratios observed for ambient hydroquinone exposures and the decrease in TRI releases indicate that current measurements to control exposure are effective.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

The environmental and toxicity profiles for hydroquinone have been well studied. Environmental effects are of low concern due to low exposure levels and the ready biodegradability and photodegradability of the substance, but processing sites such as in industrial photography, may present local environmental concern based on default modeling. While toxicity to mammalian species is associated with high doses of hydroquinone, these effects are either species- and strain-specific or minimized in humans through reduced exposure. Dermal effects in humans who use hydroquinone-containing skin products appear to be limited to individuals who misuse the products or to products which contain other active ingredients. Similar dermal effects have not been demonstrated in animals treated with similar or higher concentrations of hydroquinone. Potential hazards from dermal exposure to aqueous solutions of hydroquinone are also low based on dermal

absorption rates. Because no human health concerns have been identified, this substance has a low priority for further work.

5.2 Recommendations

An assessment of the environmental and human health effects associated with hydroquinone indicate that measures currently in effect are adequate to control potential risks. As the data base available on ecologic and human health effects is adequate for assessment of risk and no significant exposure concerns were identified following submission of additional exposure information from OECD member countries, hydroquinone has a low priority for further work. Depending on the extent of use, national action to avoid risk to the aquatic environment could be warranted on some site-specific conditions.

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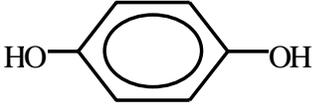
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SIDS PROFILE

1.1	CAS No.	123-31-9
1.2	CHEMICAL NAME	1,4-Benzenediol
1.5	STRUCTURAL FORMULA	
	OTHER CHEMICAL IDENTITY INFORMATION	Hydroquinone para-Dihydroxybenzene para-Benzenediol alpha-Hydroquinone
3.	SOURCES AND LEVELS OF EXPOSURE	Industrial workers are potentially exposed to hydroquinone during the manufacture, and subsequent processing as rubber antioxidants, monomer inhibitors, photographic developers, and other products. Non-industrial exposure occurs in consumers using nonprescription drugs containing 2% hydroquinone. A relatively small number of photohobbyists that develop black and white film are also potentially exposed.
3.1	PRODUCTION RANGE	40,000-45,000 tonnes per year (worldwide)
3.3	CATEGORIES AND TYPES OF USE	50% used to manufacture antioxidants, antiozonants, and inhibitors for industry (industrial) 33% in photography (industrial) 0.05% in skin creams (consumer) 11-12% for other uses such as to manufacture food antioxidants (industrial)
	Issues for discussion	

CAS NO: 123-31-9	Information Available	GLP	OECD Study	Other Study	Estimation Methods	Acceptable ?	SIDS Testing Required ?
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	Y	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degradability							
4.1.3.1 Hydrolysis	Y	N	N	Y	N	Y	N
4.1.3.2 Photodegradability	Y	N	N	N	Y	Y	N
4.3 Env. Fate/Distribution	Y	N	N	Y	N	Y	N
Env. Concentration	Y	N	N	Y	N	Y	N
OTHER STUDIES RECEIVED	Y						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	N	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	N	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	Y	N	N	Y	N	Y	N
5.6.3 Acute Toxicity Avians	Y	N	N	Y	N	Y	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	Y						
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	Y	N
Acute Inhalation	N	-	-	-	-	-	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	N	N	Y	N	Y	N
6.7 Reproductive Toxicity	Y	Y	Y	N	N	Y	N
OTHER STUDIES RECEIVED	Y						

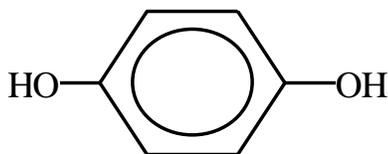
**Summary of Responses to the OECD Request for
Available Data on HPV Chemicals**

0. **General Information**

Name of Sponsor country	<u>United States of America</u>
Contact point	Mr. Charles Auer Director - Chemical Control Division Office of Toxic Substances (TS-788) U S Environmental Protection Agency 401 M Street SW Washington, DC 20460 Telephone (202) 260-3749 Fax (202) 260-8168
Name of Lead Organization	<u>U S EPA</u>

1. **Chemical Identity**

- *1.1 **CAS - number** 123-31-9
- *1.2 **Name** (Name supplied by the OECD): 1,4-Benzenediol
- 1.3 **Common Synonyms** Hydroquinone
para-Dihydroxybenzene
para-Benzenediol
I-Hydroquinone
- 1.4 **Empirical formula** C₆H₆O₂
- *1.5 **Structural formula**



1.6 **Purity of industrial product**

- 1.6.1 **Degree of Purity** (percentage by weight/volume): 98.5%
- 1.6.2 **Identity of major impurities** (Typical analysis): 1% H₂O
- 1.6.3 **Essential additives** (stabilizing agents, inhibitors, other additives), if applicable:
Not Applicable

2. Physical-Chemical Data***2.1 Melting or Decomposition Point:** 169°C (melting point)**Method** (e.g., OECD, others):**GLP:** YES []
NO [X]**Comments:** Information predates GLP regulations.**Reference:** Material Safety Data Sheet, Eastman Chemical Company.***2.2 Boiling Point** (including temperature of decomposition, if relevant).

286°C

Method (e.g., OECD, others):**GLP:** YES []
NO [X]**Comments:** Information predates GLP regulations.**Reference:** Material Safety Data Sheet, Eastman Chemical Company.***2.3 Vapor pressure**2.34 x 10⁻¹⁰ kPa at 25°C**Method** (e.g., OECD, others):**GLP:** YES []
NO [X]**Comments:** Information predates GLP regulations.**Reference:** Material Safety Data Sheet, Eastman Chemical Company.***2.4 Partition coefficient n-Octanol/water**

log Pow = 0.50-0.61 at 25°C

Method: calculated [X]
measured []**GLP:** YES []
NO [X]

- Analytical Method:** Estimation by method of Hansch and Leo
- Comments:** Information predates GLP regulations.
- Reference:** Hansch, C., and Leo, A. (1979). Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley and Sons, New York.
- *2.5 **Water solubility:**
- 73,000 mg/L at 25°C
- Method** (e.g., OECD, others): None provided
- GLP:** YES []
NO [X]
- Analytical Method:** None provided.
- Comments:** Information predates GLP regulations.
- Reference:** Sterner, J.H., Oglesby, F.L., and Anderson, B. (1947). Quinone Vapors and Their Harmful Effects. I. Corneal and Conjunctival Injury, J. Ind. Hyg. Toxicol. 29, 60-73.
- 2.6 **Flash point (liquids)** 177°C
- closed cup [] open cup [X]
- Method:** Cleveland Open Cup
- GLP:** YES []
NO [X]
- Comments:** Information predates GLP regulations.
- Reference:** Material Safety Data Sheet, Eastman Chemical Company.
- 2.7 **Flammability**
- Method** (e.g., OECD, others): ASTM D1255
- GLP:** YES []
NO [X]
- Test results:** Autoignition temperature = 499°C
- Comments:** Information predates GLP regulations.
- Reference:** Material Safety Data Sheet, Eastman Chemical Company.
- 2.8 **pH in water**

pH of 4.00 to 4.70

pKa of 9.9 for the first hydrogen ion

Method (e.g., OECD, others): None provided

GLP: YES []
NO [X]

Comments: Information predates GLP regulations.

Reference: Technical data bulletin, Eastman Chemical Products, Inc., 1975.

2.9 Other data

Density: 1.341 g/cc

Comments: Information predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Chemical Company.

3. Source of exposure

*3.1 Production levels expressed as tonnes per annum:

40,000-45,000 tonnes per year worldwide and 10,000-12,000 tonnes in the U.S.

3.2 Processes:

There are three current manufacturing processes for hydroquinone: oxidative cleavage of diisopropylbenzene, oxidation of aniline, and hydroxylation of phenol.

At Eastman Chemical Company, diisopropyl benzene is air oxidized to the intermediate diisopropylbenzene bishydroperoxide. This hydroperoxide is purified by extraction and reacted further to form hydroquinone. Process solvents are recycled. Water-insoluble impurities are incinerated, and the two water-based impurity streams are biodegraded in the plant wastewater treatment system. The purified product is isolated by filtration, and packaged. The process is almost entirely closed, continuous, computer-controlled and monitored. Less than 100 workers are potentially exposed during manufacture, materials handling, maintenance, and quality control sampling and analysis. Worker protective clothing and engineering controls, such as local exhaust and ventilation systems, are used to further prevent exposure at points in the process where exposure can occur.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

Hydroquinone can also be prepared in a closed system in which aniline is oxidized to quinone in the presence of manganese dioxide and sulfuric acid. Quinone is then reduced to hydroquinone using iron oxide. The resulting hydroquinone is crystallized and dried.

Reference: Oglesby, F.L., Sterner, J.H., and Anderson, B. (1947). Quinone Vapors and Their Harmful Effects. II. Plant Exposures Associated with Eye Injuries, J. Ind. Hyg. Toxicol. 29, 74-84.

Hydroquinone is also manufactured by hydroxylation of phenol using hydrogen peroxide as a hydroxylation agent. The reaction is catalyzed by strong mineral acids, or ferrous or cobalt salts.

Reference: Varagnat, J. (1981). Hydroquinone, resorcinol, and catechol. In: Encyclopedia of Chemical Technology, Grayson, M., ed. John Wiley & Sons, New York.

***3.3 Information concerning Uses** (including categories and types of uses expressed in percentage terms):

Virtually all the uses of hydroquinone are industrial. Approximately 25% of the hydroquinone manufactured is used as an intermediate for chemical conversion to hydroquinone-based rubber antioxidants and antiozonants. Another 25% is used as an intermediate for chemical conversion to inhibitors used to stabilize monomers. An additional 33% is used in the photographic industry including black and white photographic film, lithography, and hospital x-ray film. Other uses (11-12%) include chemical conversion to stabilizers for paints, varnishes, motor oils, and fuels, and for antioxidants for industrial use fats and oils and food.

A small amount of the hydroquinone is used by photohobbyists, and about 0.05% is used in nonprescription drugs such as skin bleaching creams. Both are considered consumer use.

3.4 Options for disposal: Incineration.

3.5 Other remarks

4. Environmental Fate and Pathways

***4.1 Degradability (biotic and abiotic)**

4.1.1 Biodegradability

Test substance: Hydroquinone

Test type, aerobic [X], anaerobic []

Test medium: Activated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test method: Similar to OECD Guideline 301D. Activated sludge was incubated in a concentration of 10 mg/L hydroquinone for 5 or 20 days.

GLP:	YES [] NO [X]
Test results:	BOD ₅ = 1.00 g/g O ₂ , COD = 1.83 g/g, THOD = 1.89 g/g BOD ₂₀ = 1.15 g/g O ₂
Comments:	Information predates GLP regulations. Additional studies listed in the attached bibliography.
Reference:	Young, R.H.F., Ryckman, D.W., and Buzzell, Jr., J.C. (1968). An Improved Tool for Measuring Biodegradability, <u>J. Water Pollut. Control Fed.</u> 40, 354-368.

4.1.2 Sewage Treatment

Test substance:	Hydroquinone
Test species:	Unacclimated, Activated sludge
Test method (e.g., OECD, others):	Eastman Kodak Company, Health and Environment Laboratories Protocol. A laboratory sewage treatment unit was used to degrade concentrations of 55-400 mg/L hydroquinone. After 8-18 hours, the total organic carbon (TOC) was determined. Similar to OECD Guideline 303A.
	<ul style="list-style-type: none"> • Type of test: IC50; Secondary Waste Treatment [X] • Other (e.g., field observation) []

GLP:	YES [] NO [X]																		
Test results:	<table> <thead> <tr> <th>[HQ] mg/L</th> <th>[HQ] removed %</th> <th>TOC removed %</th> </tr> <tr> <th>-----</th> <th>-----</th> <th>-----</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>--</td> <td>69</td> </tr> <tr> <td>55</td> <td>>99.9</td> <td>70</td> </tr> <tr> <td>100</td> <td>99.9</td> <td>87</td> </tr> <tr> <td>400</td> <td>93.1</td> <td>89</td> </tr> </tbody> </table>	[HQ] mg/L	[HQ] removed %	TOC removed %	-----	-----	-----	0	--	69	55	>99.9	70	100	99.9	87	400	93.1	89
[HQ] mg/L	[HQ] removed %	TOC removed %																	
-----	-----	-----																	
0	--	69																	
55	>99.9	70																	
100	99.9	87																	
400	93.1	89																	

Comments:	Study predates GLP regulations.
Reference:	Harbison, K.G., and Belly, R.T. (1982). The Biodegradation of Hydroquinone, <u>Environ. Toxicol. Chem.</u> 1, 9-15.

ADDITIONAL REFERENCES

Section 4.1 Degradability

Dore, M., Brunet, N., and Legube, B. (1975). Participation de différents composés organiques à la valeur des critères globaux de pollution. La Tribune du Cebadeau 374, 3-11.

Rott, B., Viswanathan, R., Freitag, D., and Korte, F. (1982). Vergleichende Untersuchung der Anwendbarkeit Verschiedener Tests zur Überprüfung der Abbaubarkeit von Umweltchemikalien. Chemosphere 11, 531-538.

Tabak, H.H., Chambers, C.W., and Kabler, P.W. (1964). Microbial metabolism of aromatic compounds. I. Decomposition of phenolic compounds and aromatic hydrocarbons by phenol-adapted bacteria. J. Bact. 87, 910-919.

4.1.3 **Stability in air** (e.g., photodegradability)

Test substance: Hydroquinone

Test method or estimation method (e.g., OECD, others): Estimation

GLP: YES []
NO [X]

Test results: $t_{1/2}$ of photodegradation = < 5 weeks in June to > 240 weeks in January

Comment: The reaction of hydroquinone with oxygen in the presence of hydroxide ions [OH⁻] in water vapor is very rapid but the rate has not been determined (NIOSH, 1978).

Reference: Devillers, J., Boule, P., Vasseur, P., Prevot, P., Steiman, R., Seigle-Murandi, F., Benoit-Guyod, J.L., Nendza, M., Grioni, C., Dive, D., and Chambon, P. (1990). Environmental and Health Risks of Hydroquinone, Ecotoxicol. Environ. Safety 19, 327-354.

4.1.3 **Stability in water** (e.g., hydrolysis)

Test substance: Hydroquinone

Test method: Oxygen utilization was measured in a Warburg respirometer at a buffered pH of 7.0, 8.0, and 9.0. Similar to OECD Guideline 111.

GLP: YES []
NO [X]

Test results:

<u>$t_{1/2}$ for O₂ utilization</u>	<u>pH</u>
111 hrs	7.0
41 hrs	8.0
0.8 hrs	9.0

Comment: No analysis of test substance. No determinations at acidic pH.

Reference: Moussavi, M. (1979). Effect of Polar Substitution on Autoxidation of Phenols, Water Res. 13, 1125-1128.

4.1.4 Identification of main mode of degradability in actual use

In photofinishing, hydroquinone is chemically converted to sulfonic acid derivatives. Wastewater sludge readily biodegrades the hydroquinone that is not already oxidized as well as hydroquinone sulfonates.

4.2 Bioaccumulation

Test substance: Hydroquinone

Test method (e.g., OECD, others): Organisms were exposed to a concentration of 0.05 mg/L ¹⁴C-Hydroquinone for 24, 72, or 120 hours. The amount of radiolabel accumulated was then determined. Similar to OECD Guideline 305E.

- Type of test: static [], semi-static [], flow-through [X]
- Other (e.g., field test) []

GLP: YES []
NO [X]

Bioaccumulation factor: The BCF-24 h in Chorella fusca (green alga) and the BCF-72 h in Leuciscus idus melanotus (golden ide) is 40.

Calculated results: BF = 40

Comments:

Reference: Freitag, D., Ballhorn, L., Geyer, H., and Korte, F. (1985). Environmental Hazard Profile of Organic Chemicals. An Experimental Method for the Assessment of the Behaviour of Organic Chemicals in the Ecosphere by Means of Simple Laboratory Test with ¹⁴C-Labelled Chemicals, Chemosphere 14, 1580-1616.

ADDITIONAL REFERENCES

Section 4.2 Bioaccumulation

Freitag, D., Geyer, H., Kraus, A., Viswanathan, R., Kotzias, D., Attar, A., Klein, W., and Korte, F. (1982). Ecotoxicological profile analysis. VII. Screening chemicals or their environmental behavior by comparative evaluation. Ecotoxicol. Environ. Safety 6, 60-81.

Geyer, H., Viswanathan, R., Freitag, D., and Korte, F. (1981). Relationship between water solubility of organic chemicals and their bioaccumulation by the alga Chlorella. Chemosphere 10, 1307-1313.

*4.3 **Transport and distribution between environmental compartments including estimated environmental concentrations and distribution pathways**

Type of transport and distribution processes between compartments (e.g., air, water, soil): Based on the low vapor pressure (see Section 2.3), transport of hydroquinone vapor to the air is expected to be minimal in the environment. Transport to soil is possible, where hydroquinone is expected to be distributed to the water compartment due to the high water solubility. Persistence is not expected because hydroquinone is readily biodegradable (see Section 4.1).

Reference: Hydroquinone/Quinone Test Rules Support Document, Dynamac Corp., 1982.

Estimation of environmental concentrations: Estimated release of hydroquinone is 10.1×10^4 kg/yr from the manufacture of methyl methacrylate.

Reference: Eimutis, E.C., Quill, R.P., and Rinaldi, G.M. (1978). Source Assessment: Noncriteria Pollutant Emissions, USEPA Industrial Environmental Research Lab.

Hydroquinone is also found in several berry plants and is formed as a byproduct from several bacteria and marine species. Approximately 5×10^4 kg of hydroquinone is generated per year in cigarette smoke.

Reference: Hydroquinone/Quinone Test Rules Support Document, Dynamac Corp., 1982.

Hydroquinone concentrations range from 0.14 to 15 $\mu\text{g/g}$ in some foods such as coffee, tea, whole wheat bread, and certain types of pears. Milk, melons, yogurt, and soft drinks have nondetectable levels of hydroquinone.

Reference: Deisinger, P.J., Hill, T.S., and English, J.C. (1994). Human Exposure to Naturally Occurring Hydroquinone, *The Toxicologist* 14, 788.

4.4 **Monitoring data** (environment)

No concentrations have been detected in wastewater, surface water, or emissions from areas in which hydroquinone is manufactured.

References: Ewing, B.B., Chian, E.S.K., Cook, J.C., Evans, C.A., Hopke, P.K., and Perkins, E.G. (1977). Monitoring to Detect Previously Unrecognized Pollutants in Surface Waters, USEPA Office of Toxic Substances.

Eimutis, E.C., Quill, R.P., and Rinaldi, G.M. (1978). Source Assessment: Noncriteria Pollutant Emissions, USEPA Industrial Environmental Research Laboratory.

Nunn, A.B., III (1978). Volatile Organic Compound Emission Inventory for Tennessee Eastman Company, USEPA Air and Hazardous Material Division.

Perry, D.L., Chuang, C.C., Jungclaus, G.A., and Warner, J.S. (1978). Identification of Organic Compounds in Industrial Effluent Discharges, USEPA Office of Toxic Substances.

Indicate whether the data are measurements of background concentrations or measurements at contaminated sites:

- air: None detected in film-developing room (Chrostek, NIOSH, 1975)

Air monitoring of the workplace environment indicated that concentrations ranged from 6.0 mg/m³ in the 1950s to 0.1 mg/m³ in the 1990s.

Pifer, J.W., Hearne, F.T., Swanson, F.A., O'Donoghue, J.L. (1995). Mortality Study of Employees Engaged in the Manufacture and Use of Hydroquinone, *Int. Arch. Occup. Environ. Health* accepted for publication.

5. Ecotoxicological Data

5.1 Toxicity to fish

*5.1.1 Results of acute tests

Test substance: Hydroquinone

Test species: Pimephales promelas (Fathead minnow)

Test method: Similar to OECD Guideline 203. Fish exposed to various concentrations for 96 hours.

- Type of test static , semi-static , flow-through
- Other (e.g., field observation)

GLP: YES
NO

Test results: LC₅₀ = > 0.4 mg/L

Comments: Study predates GLP regulations. No analysis for test substance. Additional studies listed in the attached bibliography.

Reference: Terhaar, C.J., Ewell, W.S., Dziuba, S.P., and Fassett, D.W. (1972). Toxicity of Photographic Processing Chemicals to Fish, Phot. Sci. Eng. 16, 370-377.

5.1.1 Results of acute tests (Additional study)

Test substance: Hydroquinone

Test species: Pimephales promelas (Fathead minnow)

Test method: Fish exposed to concentrations of 0.1-0.18 mg/L for 96 hours.

- Type of test static , semi-static , flow-through

- Other (e.g., field observation) []

GLP: YES []
NO [X]

Test results: LC₅₀ = 0.1-0.18 mg/L

Comments: Study predates GLP regulations. No analysis for test substance. Additional studies listed in the attached bibliography.

Reference: Environmental Effects of Photoprocessing Chemicals, National Association of Photographic Manufacturers, Inc., 1974.

5.1.1 Results of acute tests (Additional study)

Test substance: Hydroquinone

Test species: Brachydanio rerio (Zebrafish)

Test method: Fish exposed to various concentrations for 96 hours. Similar to OECD Guideline 203.

- Type of test static [X], semi-static [], flow-through []
- Other (e.g., field observation) []

GLP: YES []
NO [X]

Test results: LC₅₀ = 0.17 mg/L

Comments: Study predates GLP regulations. No analysis for test substance. Additional studies listed in the attached bibliography.

Reference: Wellens, H. (1982). Comparison of the Sensitivity of Brachydanio rerio and Leuciscus idus in the Study of the Toxicity to Fish of Chemical Compounds and Wastewaters, Z. Wasser Abwasser Forsch. 15, 49-52.

5.1.2 Results of long-term e.g., prolonged toxicity, early life stage

Test substance:

Test species:

Test method (e.g., OECD, others):

- Type of test static [], semi-static [], flow-through []

- Other (e.g., field observation)

GLP: YES
NO

Test results: No Data Available

Comments:

Reference:

ADDITIONAL REFERENCES

Section 5.1 Toxicity to Fish

Bandt, H.J. (1955). Fischereischäden durch Phenolabwässer. Wasserwirtschaft-Wassertechnik 5, 290-294.

Hodson, P.V., Dixon, D.G., and Kaiser, K.L.E. (1984). Measurement of median lethal dose as a rapid indication of contaminant toxicity to fish. Environ. Toxicol. Chem. 3, 243-254.

Juhnke, I., and Lüdemann, D. (1978). Ergebnisse der Untersuchung von 200 chemischen Verbindungen auf akute Fischtoxizität mit dem Goldorfentest. Z. Wasser Abwasser Forsch. 11, 161-164.

Sollmann, T. (1949). Correlation of the aquarium goldfish toxicities of some phenols, quinones and other benzene derivatives with their inhibition of autooxidative reactions. J. Gen. Physiol. 32, 671-679.

Tissot, A., Boule, P., Lemaire, J., Lambert, S., and Palla, J.C. (1985). Photochimie et environnement. X. Evaluation de la toxicité des produits de phototransformation de l'hydroquinone et des chlorophenols en milieu aqueux. Chemosphere 14, 1221-1230.

*5.2 Toxicity to daphnids

5.2.1 Results of acute tests

Test substance: Hydroquinone

Test species: Daphnia magna

Test method (e.g., OECD, others): Daphnids exposed for 96 hours under static conditions. Similar to OECD Guideline 202.

GLP: YES
NO

Test results: LC₅₀ = 0.05mg/L

Comments: Additional studies listed in the attached bibliography.

Reference: Environmental Effects of Photoprocessing Chemicals, National Association of Photographic Manufacturers, Inc., 1974.

5.2.1 Results of acute tests(Additional study)

Test substance: Hydroquinone

Test species: Daphnia magna

Test method (e.g., OECD, others): Daphnids exposed for 24 hours under static conditions. Similar to OECD Guideline 202.

GLP: YES []
NO [X]

Test results: LC₅₀ = 0.09 mg/L

Comments: Study predates GLP regulations. Additional studies listed in the attached bibliography.

Reference: Bringmann, G., and Kühn, R. (1977). Results of the Damaging Effect of Water Pollutants on Daphnia magna, Z. Wasser Abwasser Forsch. 10, 161-166.

5.2.1 Results of acute tests (Additional study)

Test substance: Hydroquinone

Test species: Daphnia magna

Test method (e.g., OECD, others): Daphnids exposed for 24 hours under static conditions. Similar to OECD Guideline 202.

GLP: YES []
NO [X]

Test results: EC₅₀ = 0.12 mg/L

Comments: Study predates GLP regulations. Additional studies listed in the attached bibliography.

Reference: Bringmann, G., and Kühn, R. (1982). Results of Toxic Action of Water Pollutants on Daphnia magna (Straus) Tested by an Improved Standardized Procedure, Z. Wasser Abwasser Forsch. 15, 1-6.

5.2.2 Results of long-term tests e.g., reproduction

Test substance:

Test species:**Test method** (e.g., OECD, others):**GLP:** YES []
NO []**Test results:** No Data Available**Comments:****Reference:**

ADDITIONAL REFERENCES

Section 5.2 Toxicity to Daphnids

Kühn, R., Pattard, M., Pernak, K-D., and Winter, A. (1989). Results of the harmful effects of selected water pollutants (anilines, phenols, aliphatic compounds) to *Daphnia magna*. Water Res. 23, 495-499.

5.3 Toxicity to algae*Test substance:** Hydroquinone**Test species:** Selenastrum capricornutum**Test method** (e.g., OECD, others): Organisms exposed to concentrations of 0.1-40 mg/L for 7 days. Similar to OECD Guideline 201.**GLP:** YES []
NO [X]**Test results:** Growth was initially inhibited at 1.0 mg/L but recovered after an initial lag period. A concentration of 4.0 mg/L was completely inhibitory.

EC50 (duration, e.g. 24, 48, 72 hours) = 1-4 mg/L

Maximum concentration at which no effect was observed within the period of the test: 0.4 mg/L

Minimum concentration at which effect was observed within the period of the test: 1.0 mg/L

Comments: Study predates GLP regulations. No analyses of test substance in water.**Reference:** Environmental Effects of Photoprocessing Chemicals, National Association of Photographic Manufacturers, Inc., 1974.

ADDITIONAL REFERENCES

Section 5.3 Toxicity to Algae

Bringmann, G., and Kühn, R. (1959). Vergleichende wasser-toxikologische Untersuchungen an Bakterien, Algen und Kleinkrebsen. Gesundheits-Ingenieur 4, 115-120.

Fitzgerald, G.P., Gerloff, G.C., and Skoog, F. (1952). Studies on chemicals with selective toxicity to blue-green algae. Sewage Ind. Wastes 24, 888-896.

Wängberg, S.A., and Blanck, H. (1988). Multivariate patterns of algal sensitivity to chemicals in relation to phylogeny. Ecotoxicol. Environ. Safety 16, 72-82.

5.4 Toxicity to other aquatic organisms

Test substance: Hydroquinone

Test species: Dugesia tigrina (current taxonomy: Dugesia dorotocephalo; flatworm)

Test method: Eastman Kodak Company, Health and Environment Laboratories Protocol according to Ewell, W.S., Gorsuch, J.W., Kringle, R.O., Robillard, K.A., and Spiegel, R.C. (Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Species, Environ. Toxicol. Chem. 5, 831-840, 1986). Similar to OECD Guideline 202. Organisms exposed to concentrations of 0.1 to 10 mg/L at pH 8.0.

- Type of test static [X], semi-static [], flow-through []
- Other (e.g., field observation) []

GLP: YES []
NO [X]

Test results: LC₅₀ = 2 mg/L at 96 hours

Comments: Study predates GLP regulations. Additional studies listed in the attached bibliography.

Reference: Dagon, T.J. (1975). Aquatic Toxicity Report (Unpublished report), Health and Safety Laboratory, Eastman Kodak Company.

5.4 Toxicity to other aquatic organisms (Additional study)

Test substance: Hydroquinone

Test species: Physa and Planorbis species (snails)

Test method (e.g., OECD, others): Health and Safety Laboratory protocol, Eastman Kodak Company. Six organisms were exposed to concentrations of 1, 10, or 100 mg/L hydroquinone for 96 hours. Similar to OECD Guideline 202.

GLP: YES []
NO [X]

Test results: LC₅₀ at 96 hours = 3.2 mg/L

Comments: Details of methodology not provided.

Reference: Dagon, T.J. (1975). Aquatic Toxicity Report (Unpublished report), Health and Safety Laboratory, Eastman Kodak Company.

ADDITIONAL REFERENCES

Section 5.4 Toxicity to Other Aquatic Organisms

Bringmann, G., and Kühn, R. (1959b). Wasser-toxikologische Untersuchungen mit Protozoen als Testorganismen. Gesundheits-Ingenieur 8, 239-240.

DeGraeve, G.M., Geiger, D.L., Meyer, J.S., and Bergman, H.L. (1980). Acute and embryonal toxicity of phenolic compounds to aquatic biota. Arch. Environ. Contam. Toxicol. 9, 557-568.

McLeese, D.W., Zitko, V., and Peterson, M.R. (1979). Structure-lethality relationships for phenols, anilines and other aromatic compounds in shrimp and clams. Chemosphere 2, 53-57.

Stom, D.J. (1977). Influence of polyphenols and quinones on aquatic plants and their blocking of SH-groups. Acta hydrochim. hydrobiol. 5, 291-298.

5.5 Toxicity to Bacteria

Test substance: Hydroquinone

Test species: Photobacterium phosphorium NZ11D

Test method (e.g., OECD, others): Five concentrations of test substance were incubated with the bacterium for 1 or 24 hours and the luminescence determined in a Photobioluminometer.

- Type of test: IC₅₀; Secondary Waste Treatment []
- Other (e.g., field observation) []

GLP: YES []
NO [X]

Test results: EC₅₀ for 1 hour incubation = 23.75 mg/L

EC₅₀ for 24 hour incubation = 29.25 mg/L

Comments:

Reference: McFeters, G.A., Bond, P.J., Olson, S.B., and Tchan, Y.T. (1983). A Comparison of Microbial Bioassays for the Detection of Aquatic Toxicants, Water Res. 17, 1757-1762.

ADDITIONAL REFERENCES

Section 5.5 Toxicity to Bacteria

Bringmann, G., and Kühn, R. (1977). Grenzwerte der Schadwirkung wassergefährdender Stoffe gegen Bakterien (*Pseudomonas putida*) und Grünalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest. Z. Wasser Abwasser Forsch. 10, 87-98.

Bringmann, G., and Kühn, R. (1978). Grenzwerte der Schadwirkung wassergefährdender Stoffe gegen Blaualgen (*Microcystis aeruginosa*) und Grünalgen (*Scenedesmus quadricauda*) im Zellvermehrungshemmtest. Vom Wasser 50, 45-60.

Bringmann, G., and Kühn, R. (1980). Bestimmung der biologischen Schadwirkung wassergefährdender Stoffe gegen Protozoen. II. Bakterienfressende Ciliaten. Z. Wasser Abwasser Forsch. 1, 26-31.

Lebsack, M.E., Anderson, A.D., DeGraeve, G.M., and Bergman, H.L. (1981). Comparison of bacterial luminescence and fish bioassay results for fossil-fuel process waters and phenolic constituents. In Aquatic Toxicology and Hazard Assessment, Fourth Conference, ASTM STP 737, DR Branson and KL Dickson, Eds, American Society for Testing and Materials, pp. 348-356.

Ribo, J.M., and Kaiser, K.L.E. (1983). Effects of selected chemicals to photoluminescent bacteria and their correlations with acute and sublethal effects on other organisms. Chemosphere 12, 1421-1442.

Stom, D.J., Geel, T.A., and Balayan, A.E. (1986). Effect of individual phenolic compounds and of their mixtures on luminous bacteria. Part I: Use of bacterial luminescence extinguishing for biotesting of phenols. Acta hydrochim. hydrobiol. 14, 283-292.

Trevors, J.T., and Basaraba, J. (1980). Toxicity of benzoquinone and hydroquinone in short-term bacterial bioassays. Bull. Environ. Contam. Toxicol. 25, 672-675.

***5.6 Toxicity to terrestrial organisms**

5.6.1 Toxicity to soil dwelling organisms

Test substance:

Test species:

Test method (e.g., OECD, others):

GLP:	YES [] NO []
Test result:	No Data Available
Comments:	
Reference:	
5.6.2 Toxicity to plants	
Test substance:	Hydroquinone
Test species:	Ryegrass Radish Lettuce
Test method:	Eastman Kodak Company, Health and Environment Laboratories Protocol according to Gorsuch, J.W., Kringle, R.O., and Robillard, K.A. (Chemical Effects on the Germination and Early Growth of Terrestrial Plants, <u>Plants for Toxicity Assessment, ASTM STP 1091</u> , 1990). Eighty seeds of each species were exposed to a concentration of 10, 100, or 1000 mg/L for 7 days and germination compared to control shoots.
GLP:	YES [] NO [X]
Test results:	Hydroquinone had little effect at 10 mg/L, but at 100 mg/L, the hypocotyls of radish and lettuce were inhibited. At 100 mg/L, the roots of all three plant species were also inhibited and to a greater extent. The 1000 mg/L concentration greatly reduced or prevented root growth and suppressed growth of the hypocotyls. Maximum concentration at which no effect was observed within the period of the test: 10 mg/L Minimum concentration at which effect was observed within the period of the test: 100 mg/L
Comments:	Study predates GLP regulations. No analysis of test substance.
Reference:	Dagon, T.J. (1975). Vascular Phytotoxicity Report (Unpublished report), Health and Safety Laboratory, Eastman Kodak Company.
5.6.2 Toxicity to plants (Additional study)	
Test substance:	Hydroquinone

Test species:	Corn Marigold Lettuce Radish
Test method:	Eastman Kodak Company, Health and Environment Laboratories Protocol. Ten to twenty seedlings of each species were exposed to a concentration of 10, 100, or 1000 mg/L for 7 days and growth of shoots and roots compared with seedlings grown without hydroquinone. Similar to OECD Guideline 208.
GLP:	YES [] NO [X]
Test results:	<p>The growth of corn was reduced at 1000 mg/L, but not at 100 mg/L. The leaves were brown and shriveled and root hairs missing. The growth of marigolds and lettuce were slightly reduced at 100 mg/L, and severely reduced at 1000 mg/L. Root growth of radishes was slightly inhibited at 10 mg/L, and the growth of the entire plant was slightly inhibited at 100 mg/L. Radish growth was severely inhibited at 1000 mg/L.</p> <p>Maximum concentration at which no effect was observed within the period of the test: 10 mg/L for Marigold, Lettuce, and Radish. 100 mg/L for Corn.</p> <p>Minimum concentration at which effect was observed within the period of the test: 100 mg/L for Marigold, Lettuce, and Radish. 1000 mg/L for Corn.</p>
Comments:	Study predates GLP regulations. No analysis of test substance.
Reference:	Dagon, T.J. (1975). Vascular Phytotoxicity Report (Unpublished report), Health and Safety Laboratory, Eastman Kodak Company.

5.6.3 Toxicity to birds

Test substance:	Hydroquinone in water
Test species:	Pigeon
Test method (e.g., OECD, others):	Birds were treated with a single dose of 100, 200, 300, 600, 1000, or 2000 mg/kg by oral gavage and observed for mortality and clinical signs of toxicity.
GLP:	YES [] NO [X]

Test results:	Mortality occurred at 600 mg/kg, but not at 300 mg/kg and below. A dose of 300 mg/kg produced emesis. Other symptoms were "similar to those exhibited in rats".
	LD ₅₀ = 500 mg/kg
	Maximum concentration at which no effect was observed within the period of the test (semi-chronic or chronic): 200 mg/kg
	Minimum concentration at which effect was observed within the period of the test (semi-chronic or chronic): 300 mg/kg
Comments:	Study predates GLP regulations. No analysis of test solutions. No description of individual animal clinical signs of toxicity. No measurement of body weight.
Reference:	Woodard, G.D.L. (1951). The Toxicity, Mechanism of Action, and Metabolism of Hydroquinone. Doctoral dissertation, George Washington University.

5.7 **Biological Effects Monitoring (including biomagnification)**

Test substance:

Organism or ecosystem studied:

Effects monitored:

Test results: No Data Available

Chemical analysis:

Comments: Because hydroquinone is readily biodegraded, it is not expected to biomagnify.

Reference:

5.8 **Biotransformation and kinetics in environmental species**

No Data Available

6. **Toxicological Data** (oral, dermal and inhalation, as appropriate)

*6.1 **Acute Toxicity**

6.1.1 **Acute oral toxicity**

Test substance: Hydroquinone in water

Test species/strain:	Rat/strain not specified Mouse/strain not specified
Test method :	Similar to OECD Guideline 401. Fasted rats and mice (sex not specified) were treated with a single dose of hydroquinone by gavage, and animals observed for mortality and clinical signs of toxicity over the course of 14 days.
GLP:	YES [] NO [X]
Test results:	Convulsions occurred immediately after treatment, but did not persist. Discriminating dose (for fixed dose only): LD ₅₀ (rats) = 390 mg/kg LD ₅₀ (mice) = 680 mg/kg
Comments:	Study predates GLP regulations. No analysis of dosing solutions. No description of clinical signs of toxicity for individual animals. No body weight measurements.
Reference:	Hodge, H.C., Maynard, E.A., Wilt, Jr., W.G., and Kesel, R. (1949). Studies of the Acute Toxicity of Hydroquinone (Unpublished report), Division of Pharmacology and Toxicology, University of Rochester School of Medicine and Dentistry.

6.1.1 Acute oral toxicity (Additional study)

Test substance:	Hydroquinone in water, propylene glycol, or glycerin
Test species/strain:	Rat/Priestly Rat/Sprague-Dawley Rat/Wistar
Test method :	Similar to OECD Guideline 401. Fasted and unfasted rats (sex not specified) were treated with a single dose of hydroquinone by gavage, and animals observed for mortality and clinical signs of toxicity over the course of 14 days.
GLP:	YES [] NO [X]

Test results:	<u>Strain</u>	<u>Carrier</u>	<u>Condition</u>	<u>LD₅₀</u>
	Priestly	Glycerin	Unfasted	1295 mg/kg
	Sprague	Prop Glycol	Unfasted	1090 mg/kg
	Sprague	Water	Unfasted	1182 mg/kg
	Sprague	Glycerin	Unfasted	1081 mg/kg
	Sprague	Prop Glycol	Fasted	323 mg/kg
	Wistar	Prop Glycol	Unfasted	731 mg/kg
	Wistar	Prop Glycol	Fasted	298 mg/kg

Comments: Study predates GLP regulations. No analysis of dosing solutions. No description of clinical signs of toxicity. No body weight measurements.

Reference: Carlson, A.J., and Brewer, N.R. (1953). Toxicity Studies on Hydroquinone, *Proc. Soc. Exper. Biol. Med.* 84, 684-688.

6.1.1 Acute oral toxicity (Additional study)

Test substance: Hydroquinone in water

Test species/strain: Rat/Osborne-Mendel
Mice/Swiss

Test method : Similar to OECD Guideline 401. Male and female fasted rats or unfasted mice were treated with a single dose of hydroquinone by gavage, and animals observed for mortality and clinical signs of toxicity over the course of 14 days.

GLP: YES []
NO [X]

Test results: There was a rapid onset of twitching of the eyelids and of the muscles around the head and neck. This progressed to tremors of "virtually all muscles" and occasionally convulsions. Respiration was impeded and death occurred within a few hours. Animals receiving lower doses recovered from tremors and exhibited no other symptoms.

LD₅₀ = 302 mg/kg (rats); 390 mg/kg (mice)

Comments: Study predates GLP regulations. No analysis of dosing solutions. No body weight measurements.

Reference: Woodard, G.D.L. (1951). The Toxicity, Mechanism of Action, and Metabolism of Hydroquinone. Doctoral dissertation, George Washington University.

6.1.2 Acute inhalation toxicity

Test substance:

Test species/strain:**Test method:**

GLP: YES []
NO []

Test results: No Data Available

LC₅₀:

Comments:**Reference:**6.1.3 **Acute dermal toxicity**

Test substance: Hydroquinone

Test species/strain: Guinea pig/strain not designated

Test method: Laboratory of Industrial Medicine Protocol, Eastman Kodak Company. Similar to OECD Guideline 402. Quantities (0.25, 0.5, or 1.0 g/kg) of hydroquinone were applied topically to three guinea pigs, one dose level per animal, and the application sites wrapped for 24 hours under occlusive patch. Animals were observed for mortality, weight gain, and irritation for 14 days.

GLP: YES []
NO [X]

Test results: No mortality occurred and all animals gained weight. Slight to moderate edema and moderate erythema was observed 24 hours after dosing, but not thereafter.

LD50: > 1 g/kg

Comments: Results from repeated dose dermal toxicity studies in mice and rats (see Section 6.4) indicated no toxicity or mortality at doses of 3840 mg/kg in rats and 4800 mg/kg in mice.

Reference: Toxicity Report (Unpublished report), Laboratory of Industrial Medicine, Eastman Kodak Company, 1971.

6.2 **Corrosiveness/Irritation**6.2.1 **Skin Irritation**

Test substance:

Test species/strain:**Test method:**

GLP: YES []
NO []

Test results: No Data Available

Comments: See Section 6.1.3. Slight erythema was observed in guinea pigs that were exposed for 24 hours. No irritation was observed 7 days after treatment.

Reference:6.2.2 **Eye Irritation**

Test substance: Hydroquinone

Test species/strain: Rabbit/strain not designated

Test method (e.g., OECD, others): Several crystals of hydroquinone powder (no amount provided) were placed into the right eye of two rabbits. The treated eye of one animal was washed, while the treated eye of the other animal remained unwashed. Irritation was scored at 1, 24, 48 hours, and 14 days after treatment.

GLP: YES []
NO [X]

Test results: Slight erythema of the palpebra developed after 1 hour in both washed and unwashed eyes. Erythema of the nictitating membrane was also evident in the unwashed eye at 1 hour. By 24 hours, the washed eye appeared normal, but the unwashed eye continued to demonstrate slight erythema of the palpebra, orbital, and nictitating membranes. Erythema of the nictitating membrane persisted to 48 hours after instillation but was not observed 14 days after treatment.

Comments: Study predates GLP regulations.

Reference: Toxicity Report (Unpublished report), Laboratory of Industrial Medicine, Eastman Kodak Company, 1971.

6.3 **Skin sensitisation**

Test substance: Hydroquinone (2% in 0.9% saline for injection and 10% in distilled water for dermal induction; 5% in distilled water for challenge)

Test species/strain: Guinea Pig/strain not specified

Test method:	Maximization test in compliance with OECD Guideline 406.
GLP:	YES [] NO [X]
Test results:	Number of animals with skin reaction at challenge: 7/10 Number of animals with skin reaction in control group at challenge: Not indicated.
Comments:	Study not intended to comply with GLP regulations. Reaction in control animals assumed to be negative.
Reference:	Goodwin, B.F.J., Crevel, R.W.R., and Johnson, A.W. (1981). A Comparison of Three Guinea-Pig Sensitization Procedures for the Detection of 19 Reported Human Contact Sensitizers, <u>Contact Derm.</u> 7, 248-258.

6.3 Skin sensitisation (Additional study)

Test substance:	Hydroquinone (2.5% in 0.9% saline for injection; challenge with 1.0% in saline by intradermal injection and 30% in distilled water for topical challenge)
Test species/strain:	Guinea Pig/strain not specified
Test method:	Draize pocedure in compliance with OECD Guideline 406.
GLP:	YES [] NO [X]
Test results:	Number of animals with skin reaction at challenge: 3/10 Number of animals with skin reaction in control group at challenge: Not indicated.
Comments:	Study not intended to comply with GLP regulations. Reaction in control animals assumed to be negative.
Reference:	Goodwin, B.F.J., Crevel, R.W.R., and Johnson, A.W. (1981). A Comparison of Three Guinea-Pig Sensitization Procedures for the Detection of 19 Reported Human Contact Sensitizers, <u>Contact Derm.</u> 7, 248-258.

*6.4 Repeated dose toxicity

Test substance:	Hydroquinone (>99%)
Test species/strain:	Sprague-Dawley rats

Test method:	According to USEPA TSCA Guideline 40 CFR 798.6050. Neurohistopathology was conducted on the forebrain, cerebrum, midbrain, cerebellum, pons, medulla oblongata, cervical spinal cord swelling, lumbar spinal cord swelling, cervical and lumbar dorsal root, dorsal-ventral spinal roots, sciatic nerve and tibial nerve. The kidneys of the high-dose and control male rats were also processed for histopathology. Animals received 0, 20, 64, or 200 mg/kg in distilled water by gavage for 13 weeks (5 days per week).
GLP:	YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
Test results:	No mortality occurred. Tremors and reduced home-cage activity were observed in mid- and high-dose groups immediately after dosing with the incidence increased in a dose-dependent manner. All treated groups were noted with brown discolored urine. No differences in body weight or feed consumption were noted. No differences in brain or kidney weight were observed. No morphologic lesions associated with treatment were observed.
Comments:	
Reference:	Bernard, L.G. (1988). Subchronic Oral Toxicity Study of Hydroquinone in Rats Utilizing a Functional-Observational Battery and Neuropathology to Detect Neurotoxicity (Unpublished report TX-88-78), Eastman Kodak Company.

6.4 Repeated dose toxicity (Additional study)

Test substance:	Hydroquinone (>99%) in ethanol
Test species/strain:	Fischer 344 rats B6C3F1 mice
Test method:	Groups of five rats per sex were treated with 0, 240, 480, 960, 1920, or 3840 mg/kg by dermal application, while mice were treated with 0, 300, 600, 1200, 2400, or 4800 mg/kg by dermal application. Animals were given 12 doses over 14 days. Animals were observed daily for clinical signs of toxicity. Body weights were measured on Days 0, 7, and 14. All procedures were in accordance with the NTP Statement of Work.
GLP:	YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
Test results:	All animals survived treatment. The body weights of male rats at the highest dose level were reduced by 6% relative to the controls. The body weights of female rats and all mice were

comparable to controls. There were no clinical signs of toxicity in either species.

Comments: Feed consumption or water consumption were not measured. Tissues were not evaluated histologically. Study conducted in 1981. Animals were group housed.

Reference: Toxicology and Carcinogenesis Studies of Hydroquinone in F344/N Rats and B6C3F1 Mice (Technical report No. 366), National Toxicology Program, 1989.

6.4 Repeated dose toxicity (Additional study)

Test substance: Hydroquinone (>99%) in corn oil

Test species/strain: Fischer 344 rats

Test method: Groups of 10 animals per sex were treated with 0, 25, 50, 100, 200, or 400 mg/kg by gavage for 13 weeks (5 days per week). Animals were observed twice daily for clinical signs of toxicity. Body weights were measured weekly. Histological examination performed on tissues from all animals in the 0, 200, and 400 mg/kg dose groups. Target tissues (liver, kidneys, and stomach in male rats; and kidneys in female rats) were examined in the 100 mg/kg dose group. All procedures were in accordance with the NTP Statement of Work. Similar to OECD Guideline 408.

GLP: YES []
NO [X]

Test results: All rats in the 400 mg/kg group and 3/10 female rats in the 200 mg/kg group died on test. Animals at 200 mg/kg were lethargic after 10 weeks of dosing, and female rats exhibited tremors and occasional convulsions. No treatment-related clinical signs of toxicity were observed in other dose groups. Body weights of male rats given 200 mg/kg were 9% less than in the control group. All other groups, including the 200 mg/kg female rats, had body weights that were comparable to the control group. Absolute and relative (to body weight) liver weights in all treated male groups were lower than in the control group. In female rats, absolute and relative liver weights were significantly higher in the 50, 100, and 200 mg/kg group compared with the control group. Hemorrhage, intra-abdominal bleeding, and gastrointestinal inflammation were evident at necropsy of animals in the 400 and 200 mg/kg groups. Inflammation and epithelial hyperplasia occurred in 4/10 males and 1/10 females at 200 mg/kg, but not in other groups. Toxic nephropathy was observed in 7/10 male and 6/10 female rats at 200 mg/kg and 1/10 females at 100 mg/kg. The severity ranged from

moderate to marked in males and was less severe in females. Tubular cell degeneration and regeneration in the cortex was evident.

Comments: Feed consumption or water consumption were not measured. Study conducted in 1981. Animals were group-housed. Sprague-Dawley rats treated with 200 mg/kg hydroquinone by gavage for 13 weeks did not demonstrate renal toxicity or unusual lesions in the kidney (see Section 6.8).

Reference: Toxicology and Carcinogenesis Studies of Hydroquinone in F344/N Rats and B6C3F1 Mice (Technical report No. 366), National Toxicology Program, 1989.

6.4 Repeated dose toxicity (Additional study)

Test substance: Hydroquinone (>99%) in corn oil

Test species/strain: B6C3F1 mice

Test method: Groups of 10 animals per sex were treated with 0, 25, 50, 100, 200, or 400 mg/kg by gavage for 13 weeks (5 days per week). Animals were observed twice daily for clinical signs of toxicity. Body weights were measured weekly. Histological examination performed on tissues from all animals in the 0, 200, and 400 mg/kg dose groups. All procedures were in accordance with the NTP Statement of Work. Similar to OECD Guideline 408.

GLP: YES []
NO [X]

Test results: Eight male and eight female mice in the 400 mg/kg group, and 2/10 male mice in the 200 mg/kg group, died on test. One death at 200 mg/kg was attributed to gavage error. All treated male mice, and all females in the top three dose groups, were lethargic after dosing. All mice in the 400 mg/kg group exhibited tremors followed by convulsions. Body weights of treated mice were comparable to the control group. Absolute and relative (to body weight) liver weight in all treated male groups were higher than in the control group. In female mice, absolute liver weight in the 100 and 400 mg/kg groups, and relative liver weight in the 200 and 400 mg/kg groups, were significantly higher compared with the control group. Ulceration, inflammation, or epithelial hyperplasia of the forestomach occurred in 3/10 males and 2/10 females at 400 mg/kg, and 1/10 females at 200 mg/kg. No other lesions were noted.

Comments: Feed consumption or water consumption were not measured. Study conducted in 1981. Animals were group-housed.

Reference: Toxicology and Carcinogenesis Studies of Hydroquinone in F344/N Rats and B6C3F1 Mice (Technical report No. 366), National Toxicology Program, 1989.

6.4 Repeated dose toxicity (Additional study)

Test substance: Hydroquinone (>99%) in an oil-in-water emulsion cream

Test species/strain: Fischer 344 rats

Test method: Groups of 20 male and female Fischer-344 rats were topically treated with 0, 2.0, 3.5, or 5.0% (w/w) of hydroquinone in an oil-in-water emulsion cream. The formulation of the cream chosen was representative of commercially available preparations sold in the United States of America and the European Union. The high concentration of 5.0% was selected as the highest concentration which could be administered under occlusion without exceeding the maximum tolerated dose or altering the barrier properties of the skin. Preparations were applied to the shaved skin of the back under semi-occluded patch for 6 hr/day, 5 days/week for 13 weeks. Animals were observed daily for clinical signs of toxicity. Signs of dermal irritation were scored daily during Weeks 1, 2, 6, 7, 12, and 13 or once per week at other times. Body weights and feed consumption were measured at least once weekly. Water consumption was measured three times a week during Weeks 1, 2, 6, 7, 12, and 13. After 13 weeks of treatment, animals were euthanatized and blood collected for clinical pathology. The liver, kidneys, testes/ovaries, brain, lungs, adrenal glands, and thymus were weighed. All tissues were preserved in fixative. The bone marrow (sternum), kidneys, liver, lymph nodes, spleen, thymus, thyroid gland, skin (application site and control site), Zymbal's gland, and gross lesions from the 5.0% and control groups, and gross lesions from all groups were examined microscopically. Similar to OECD Guideline 411.

GLP: YES []
NO []

Test results: One animal died on the first day of dosing apparently because the wrappings were too tight. All other animals survived to their scheduled times of necropsy. Hydroquinone exposure was associated with increased incidence of scaly skin, a general brown discoloration of the skin (primarily in male rats), and brown spots at the application site. These conditions were observed in control and hydroquinone-treated groups suggesting that they were related to the treatment procedures such as repeated shaving or the use of a semi-occlusive patch. Erythema at the application site was also observed primarily

in the hydroquinone-treated groups, but irritation was not observed after 2 days of recovery. No significant differences in body weight were noted among groups. Feed consumption by the 3.5 and 5.0% male rats on Day 4 were significantly ($p \leq 0.05$) lower than by the control group, but no differences were noted among female groups. Water consumption by treated rats was generally within 10% of consumption by control rats. No ophthalmic lesions were noted at the end of the study. After 13 weeks of treatment, animals were euthanatized and blood collected for clinical pathology. No biologically significant changes occurred in hematology or red blood cell morphology. Changes in serum chemistries among male groups were not considered to be biologically meaningful, and no changes in serum chemistries were noted among female groups. No differences in absolute or relative organ weight were noted. No hydroquinone-related gross or microscopic lesions were noted. Based on these results, dermal application of 5.0% hydroquinone in a oil-in-water emulsion cream (73.9 mg/kg/day in males and 109.6 mg/kg/day in females) under occlusion produced only transient minor irritation of the skin. Based on erythema in all hydroquinone-treated groups, a no-observable-effect level (NOEL) could not be determined. Based on the lack of adverse systemic effects or histopathology, the no-observable-adverse-effect level (NOAEL) was 5.0% hydroquinone.

Comments:

At the beginning of Weeks 3, 6, and 13, an additional five animals per sex per group were used for cell proliferation in the kidneys. Osmotic pumps filled with bromodeoxyuridine (BrdU) were implanted 3 days prior to necropsy. On the third day post-implantation, animals were placed into metabolism cages to collect urine for analysis. No biologically significant changes were observed in the urine of treated rats. On the fourth day post-implantation, the animals were euthanatized and the kidneys and a section of small intestine were removed for histology and staining with BrdU antibody. One kidney from each animal was evaluated for cell proliferation. Evaluation of cell proliferation indicated only a modest, transient increase in replication of P1 cells of 5.0% male rats at 3 Weeks, but not thereafter, and an increase in distal tubule cell (other cells) replication in female 3.5 and 5.0% rats at 13 Weeks. These increases were not considered to be biologically significant.

Reference:

David, R. (1994). NDMA High HQ Formulation Cream: A Thirteen-Week Dermal Toxicity and Cell Proliferation Study in the Rat (unpublished report), Nonprescription Drug Manufacturers Association.

***6.5 Genetic Toxicity**

6.5.1 Bacterial test

Test substance:	Hydroquinone in DMSO												
Test species/strain:	<u>Salmonella typhimurium</u> /TA-98, TA-100, TA-1535, and TA-1537												
Test method:	Bacteria/test substance mixtures were incubated with a 30% concentration of S-9 from rats or hamsters treated with Aroclor 1254. Similar to OECD Guideline 471.												
GLP:	YES [<input type="checkbox"/> NO [<input checked="" type="checkbox"/>												
Test results:	<p>Minimum concentration of test substance at which toxicity to bacteria was observed:</p> <p>with metabolic activation: >666 Tg/plate without metabolic activation: 333 Tg/plate</p> <p>Concentration of the test compound resulting in precipitation: NA</p> <p>Genotoxic effects:</p> <table> <tr> <td></td> <td>+</td> <td>?</td> <td>-</td> </tr> <tr> <td>with metabolic activation:</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> </tr> <tr> <td>without metabolic activation:</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> </tr> </table>		+	?	-	with metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	without metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
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with metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>										
without metabolic activation:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>										
Comments:	Conducted under Government contract. Not under GLP regulations. Additional studies listed in the attached bibliography.												
Reference:	Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). Salmonella Mutagenicity Test Results For 250 Chemicals, <u>Environ. Mut. Suppl.</u> 1, 3-142.												

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Section 6.5.1 Bacterial Tests

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Florin, I., Rutberg, L., Curvall, M., and Enzell, C. R. (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 18, 219-232.

Gocke, E., King, M-T., Eckardt, K., and Wild, D. (1981). Mutagenicity of cosmetics ingredients licensed by the European community. *Mutat. Res.* 90, 91-109.

Koike, N., Haga, S., Ubukata, N., Sakurai, M., Shimizu, H., and Sato, A. (1988). Mutagenicity of benzene metabolites by fluctuation test. *Jpn. J. Ind. Health* 30, 475-480.

Rapson, W. H., Nazar, M. A., and Butsky, V. V. (1980). Mutagenicity produced by aqueous chlorination of organic compounds. *Bull. Environ. Contam. Toxicol.* 24, 590-596.

Sakai, M., Yoshida, D., and Mizusaki, S. (1985). Mutagenicity of polycyclic aromatic hydrocarbons and quinones on *salmonella typhimurium* TA97. *Mutat. Res.* 156, 61-67.

6.5.2 Non-bacterial in vitro test

Test substance: Hydroquinone in DMSO

Type of cell used: Chinese Hamster Ovary

Test method (e.g., OECD, others): Populations of 50-100 cells were incubated in concentrations of 0, 5, 7.5, 10, or 20 Tg/ml for 10.5 hours in the absence of S9 and the cells arrested in metaphase with colcemid. Cells (100) were also incubated in concentrations of 0, 150, 450, or 600 Tg/ml for 10.5 hours in the presence of S9 and the cells arrested in metaphase with colcemid. The cells were stained and the number of chromosomal aberrations counted. Similar to OECD Guideline 403.

GLP: YES []
NO [X]

Test results:

Lowest Concentration producing cell toxicity: Not determined

with metabolic activation: µg/mL

without metabolic activation: µg/mL

Genotoxic effects:

	+ ? -
with metabolic activation:	[X] [] []
without metabolic activation:	[] [] [X]

Comments: Conducted under Government contract. Not under GLP regulations. Additional studies listed in the attached bibliography.

Reference: Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpou, J., Margolin, B.H., Resnick, M.A., Anderson, B., Zeiger, E. (1987). Chromosome Aberrations and Sister Chromatid Exchanges in Chinese Hamster Ovary

Cells: Evaluations of 108 Chemicals, Environ. Mol. Mutagen. 10(Suppl), 1-175.

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Section 6.5.2 Non-bacterial *in vitro* Tests

Ciranni, R., and Adler, I. (1991). Clastogenic effects of hydroquinone: induction of chromosomal aberrations in mouse germ cells. Mutat. Res. 263, 223-229.

Erexson, G. L., Wilmer, J. L., and Kligerman, A. D. (1985). Sister chromatid exchange induction in human lymphocytes exposed to benzene and its metabolites *in vitro*. Cancer Res. 45, 2471-2477.

Gocke, E., Wild, D., Eckhardt, K., and King, M.-D. (1983). Mutagenicity studies with the mouse spot test. Mutat. Res. 117, 201-212.

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Morimoto, K., and Wolff, S. (1980). Increase of sister chromatid exchanges and perturbations of cell division kinetics in human lymphocytes by benzene metabolites. Cancer Res. 40, 1189-1193.

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Painter, R. B., and Howard, R. (1982). The HeLa DNA-synthesis inhibition test as a rapid screen for mutagenic carcinogens. Mutat. Res. 92, 427-437.

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Parmentier, R., and Dustin, P. (1948). Early effects of hydroquinone on mitosis. Nature 171, 527-528.

Parry, J.M., Parry, E.M., Warr, T., Lynch, A., and James, S. (1990). The detection of aneugens using yeast and cultured mammalian cells. Mutation and the Environment, Part B, Wiley-Liss, New York, 247-266.

Pellack-Walker, P., and Blumer, J. L. (1986). DNA damage in L5178YS cells following exposure to benzene metabolites. Mol. Pharmacol. 30, 42-47.

Pellack-Walker, P., Walker, J. K., Evans, H. H., and Blumer, J. L. (1985). Relationship between oxidation potential of benzene metabolites and their inhibitory effect on DNA synthesis in L5178YS cells. Mol. Pharmacol. 28, 560-566.

6.5.3 Non-bacterial test in vivo

Test substance: Hydroquinone in water

Test species/strain: CD-1 mice

Test method (e.g., OECD, others): Animals (3 per group) were given a single dose of 0, 40, 60, or 80 mg/kg by intraperitoneal injection and euthanatized 18 hours after injection. Bone marrow was collected and 3000 polychromatic cells scored from each animal. Similar to OECD Guideline 474.

GLP: YES []
NO [X]

Test results: Lowest dose producing toxicity: Not determined

Effect on Mitotic Index or P/N Ratio:

<u>Dose</u>	<u>P/N Ratio</u>
0	0.938
40	0.903
60	0.983
80	0.961

Genotoxic effects

+ ? -
[X] [] []

Comments: Study not intended to comply with GLP regulations. Additional studies listed in the attached bibliography.

Reference: Barale, R., Marrazzini, A., Betti, C., Vangelisti, V., Loprieno, N., and Barrai, I. (1990). Genotoxicity of Two Metabolites of

Benzene: Phenol and Hydroquinone Show Strong Synergistic Effects In Vivo, Mutat. Res. 244, 15-20.

6.5.3 Non-bacterial test in vivo (Additional study)

Test substance: Hydroquinone in water

Test species/strain: CD-1 mice

Test method (e.g., OECD, others): Animals (4 per group) were given a single dose of 80 mg/kg by oral gavage and euthanized 0-48 hours after treatment. Bone marrow was collected and 3000 polychromatic cells scored from each animal. Similar to OECD Guideline 474.

GLP: YES
NO

Test results:

Lowest dose producing toxicity: toxicity was observed at this dose.

Effect on Mitotic Index or P/N Ratio:

Harvest Time (hrs)	Micronuclei	P/N Ratio
0	< 2%	> 1.2
18	~ 4%	> 1.2
24	~ 2%	>1.2
42	~ 4%	0.6
48	~ 4%	> 1.2

Genotoxic effects

+ ? -

Comments: Study not intended to comply with GLP regulations. Additional studies listed in the attached bibliography.

Reference: Ciranni, R., Barale, R., Ghelardini, G., and Loprieno, N. (1988). Benzene and the genotoxicity of its metabolites. II. The effect of the route of administration on the micronuclei and bone marrow depression in mouse bone marrow cells. Mutat. Res. 209, 23-28.

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Barale, R., Ciranni, R., Casini, D., and Loprieno, N. (1987). Clastogenic activity of benzene and its metabolites in mice. Mutat. Res. 181, 322.

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Chatterjee, P., and Sharma, A. (1972). Effect of phenols on nuclear division in *Chara zeylanica*. The Nucleus 15, 214-218.

Ciranni, R., Barale, R., Marrazzini, A., and Loprieno, N. (1988). Benzene and the genotoxicity of its metabolites. I. Transplacental activity in mouse fetuses and in their dams. Mutat. Res. 208, 61-67.

Gad-El-Karim, M. M., Ramanujam, V. S., and Legator, M. (1986). Correlation between the induction of micronuclei in bone marrow by benzene exposure and the excretion of metabolites in urine of CD-1 mice. Toxicol. Appl. Pharmacol. 85, 464-477.

Gad-El-Karim, M. M., Ramanujam, V. S., Ahmed, A. E., and Legator, M. S. (1985). Benzene myeloclastogenicity: a function of its metabolism. Am. J. Ind. Med. 7, 475-484.

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Marrazzini, A., Betti, C., Barale, R., Bernacchi, F., and Loprieno, N. (1991). Cytogenetic effects of possible aneuploidizing agents. Mutat. Res. 252, 195-196.

Shimada, H., Sato, T., and Takayama, S. (1988). Induction of micronuclei by benzene and its metabolites. Tokyo: Research Institute of Daiichi Seiyaku Co., Ltd.

Tunek, A., Hogstedt, B., and Olofsson, T. (1982). Mechanism of benzene toxicity, effects of benzene and benzene metabolites on bone marrow cellularity, number of granulopoietic stem cells and frequency of micronuclei in mice. Chemical-Biological Interactions 39, 129-138.

Tunek, A., Olofsson, T., and Berlin, M. (1981). Toxic effects of benzene and benzene metabolites on granulopoietic stem cells and bone marrow cellularity in mice. Toxicol. Appl. Pharmacol. 59, 149-156.

Xu, W., and Adler, I. (1990). Clastogenic effects of known and suspected spindle poisons studied by chromosome analysis in mouse bone marrow cells. Mutagenesis 5, 371-374.

Xu, W., Miller, B., Kliesch, U., and Adler, I. (1989). Spindle inhibition and chromosomal breakage in mouse bone marrow by econazole (EZ) and hydroquinone (HQ). Mutat. Res. 216, 305.

6.6 Carcinogenicity**Test substance:** Hydroquinone**Test species/strain:** Sprague-Dawley Rats**Test method** (e.g., OECD, others): Groups of 20 rats per group were treated with 0, 0.1, 0.5, and 1.0% hydroquinone in a synthetic diet of skim milk, lard, whole wheat, and salt for 103 weeks. Diets were prepared weekly. Body weights were measured periodically. Hematology was conducted at termination. Histologic examinations of the liver, omentum, kidney, spleen, heart, lung, bone marrow, stomach wall, pancreas, adrenal, subperitoneal and intramuscular abdominal fat were performed after 103 weeks.**GLP:** YES []
NO [X]**Test results:** No treatment-related changes in hematology were observed. Survival was not impacted by treatment. No differences in terminal body weight were observed. However, body weights of mid- and high-dose rats were lower than body weights of the controls during the first 4 weeks on test. Histopathology indicated "atrophy of the liver cord cells, lymphoid tissue of the spleen, adipose tissue, and striated muscle together with superficial ulceration and hemorrhage of the stomach mucosa".**Comments:** Feed consumption or water consumption were not measured. Animals were not observed for clinical observations. No analysis of the test substance in the diet. Non-standard diet used.**Reference:** Carlson, A.J., and Brewer, N.R. (1953). Toxicity Studies on Hydroquinone, *Proc. Soc. Exper. Biol. Med.* 84, 684-688.**6.6 Carcinogenicity (Additional study)****Test substance:** Hydroquinone in deionized water**Test species/strain:** Fischer 344 Rats
B6C3F1 Mice**Test method** (e.g., OECD, others): Groups of 65 rats per sex were treated with 0, 25, 50 mg/kg for 103 weeks (5 days per week). Groups of 64-65 mice per sex were treated with 0, 50, 100 mg/kg for 103 weeks (5 days per week). Animals were observed twice daily for clinical signs of toxicity. Body weights were measured weekly for the first 13 weeks, and monthly thereafter. Hematology and clinical chemistry was conducted after 15 months on test. Histologic examinations of all tissues of rats, and high-dose and control mice, were performed after 104

weeks. All procedures in accordance with the NTP Statement of Work. Similar to OECD Guideline 451.

GLP: YES [X]
NO []

Test results: No compound-related clinical signs of toxicity and no treatment-related changes in clinical pathology were observed. Survival was not impacted by treatment.

The body weights of treated male rats were significantly (9-12%) lower than body weights of the controls. Body weights of female rats were comparable. Relative (to body weight) brain, kidney, and liver weights in the 50 mg/kg male group were significantly higher than in the control group. Relative brain weight in the 25 mg/kg male group was also significantly higher. No differences were evident among the female groups. Treatment-related lesions occurred in the kidneys with a significant increase in the severity of spontaneous nephropathy in high-dose male rats. In addition, a dose-related increase in animals with single renal tubular adenomas occurred in the low- and high-dose male groups. Other lesions in male rats were not considered toxicologically significant or treatment-related. In females, a dose-related increase in the incidence of mononuclear leukemia was noted. This lesion was considered to be the proximate cause of death in many treated female rats.

The body weights of treated male mice were 4-6% lower than body weights of the controls, and body weights of treated female mice were 3-13% lower than controls. No significant differences in body weight were noted. Relative liver weights of high-dose male and female mice, and low-dose male mice, were significantly higher than in the control group. Treatment-related increases in non-neoplastic lesions (anisokaryosis, syncytial alteration, and basophilic focus) of the liver occurred in male mice. In female mice, there was a treatment-related increase in the incidence of hepatocellular adenomas. Both male and female treated mice had an increased incidence of follicular cell hyperplasia of the thyroid gland, although the effect was not dose-related. All other lesions were not considered to be treatment-related.

Comments: Feed consumption or water consumption were not measured. Animals were group-housed.

Reference: Toxicology and Carcinogenesis Studies of Hydroquinone in F344/N Rats and B6C3F1 Mice (Technical report No. 366), National Toxicology Program, 1989.

6.6 Carcinogenicity (Additional study)

Test substance: Hydroquinone (0.8% in the diet)

Test species/strain:	Fischer 344 Rats B6C3F1 Mice
Test method (e.g., OECD, others):	Groups of 30 rats per sex were treated with 0.8% hydroquinone in the diet for 103 weeks. Groups of 30 mice per sex were treated with the same diet 96 weeks. Animals were observed twice daily for clinical signs of toxicity. Body weights were measured weekly for the first 13 weeks, and monthly thereafter. Feed and water consumption were measured for two days prior to each weighing. The liver and kidneys were weighed at necropsy. Histologic examinations of all tissues were performed after 104 weeks. Similar to OECD Guideline 451.
GLP:	YES [] NO [X]
Test results:	<p>No compound-related clinical signs of toxicity. Survival was not impacted by treatment.</p> <p>Body weight gains of treated rats and male mice were significantly lower than of the controls. However, only terminal body weights of female mice and female rats were significantly lower than of the control groups. Feed and water consumption of treated groups were comparable to the control groups. Absolute and relative (to body weight) liver and kidney weights in treated male rats were significantly higher than in the control group. Relative liver and kidney weights of female treated mice, and relative kidney weights of female rats, were also significantly higher than in the control groups. Chronic nephropathy occurred in treated rats with a significant increase in the severity compared with control rats. In addition, treated male rats had significantly increased incidences of tubular adenomas, tubular hyperplasia, and epithelial hyperplasia of the renal papilla. The hyperplasia of the renal papilla was considered to be reflective of the chronic nephropathy. Other lesions in male rats were not considered toxicologically significant or treatment-related. No changes in the forestomach were noted.</p> <p>In mice, a treatment-related increase in renal tubular hyperplasia was noted in treated males compared with controls. Centrilobular hypertrophy of the hepatocytes was observed in treated male mice, and there was an increased incidence of hepatocellular adenomas and foci of cellular alteration, but not hepatocellular carcinoma. An increase in the incidence of hyperplasia of the forestomach was observed in both male and female treated mice compared with control mice.</p>
Comments:	Animals were group-housed.

Reference: Shibata, M.A., Hirose, M., Tanaka, H., Asakawa, E., Shirai, T., and Ito, N. (1991). Induction of Renal Cell Tumors in Rats and Mice, and Enhancement of Hepatocellular Tumor Development in Mice after Long-term Hydroquinone Treatment, Jpn. J. Cancer Res. 82, 1211-1219.

ADDITIONAL REFERENCES INTO MECHANISMS OF CELLULAR EVENTS

Reddy, M. V., Bleicher, W. T., Blackburn, G. R., and Mackerer, C. R. (1990). DNA adduction by phenol, hydroquinone, or benzoquinone *in vitro* but not *in vivo*: nuclease P1-enhanced ³²P-postlabeling of adducts as labeled nucleoside biphosphates, dinucleotides and nucleoside monophosphate. Carcinogenesis 11, 1349-1357.

Boatman, R.J., English, J.C., Perry, L.G., and Bialecki, V.E. (1992). Indicators of nephrotoxicity for hydroquinone and for 2-(glutathion-S-yl)hydroquinone in Fischer-344 and Sprague-Dawley rats and in B6C3F1 mice (Unpublished report), Health and Environment Laboratories, Eastman Kodak Company.

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English, J.C., Perry, L.G., Vlaovic, M., Moyer, C., and O'Donoghue, J.L. (1994). Measurement of cell proliferation in the kidneys of Fischer 344 and Sprague-Dawley rats after gavage administration of hydroquinone, Fundam. Appl. Toxicol. 23, 397-406.

*6.7 Reproductive and Developmental toxicity

6.7.1 Reproductive toxicity

Test substance: Hydroquinone (99%) in distilled water

Test species/strain: Sprague-Dawley Rats

Test method (e.g., OECD, others): OECD Guideline 416. Animals treated with 0, 15, 50, or 150 mg/kg/day by gavage.

GLP: YES [X]
NO []

Test results: NOEL for P generation = 15 mg/kg/day
NOEL for F1 generation = 150 mg/kg/day
NOEL for F2 generation = 150 mg/kg/day

Maternal and Paternal general toxicity: At the 15 and 50 mg/kg/day dose levels, no adverse effects of treatment were evident from mortality, body weight, or feed consumption data. Tremors were observed in one male at 50 mg/kg/day, and in several males and females in the 150 mg/kg dose groups.

Reproductive toxicity observed in parental animals (fertility, gestation, reproductive organ toxicity, etc.): No adverse effects were seen in body weight, sex distribution, survival, or gross pathology of pups delivered.

Reproductive toxicity observed in offspring (weights of litter, postnatal growth, viability, etc.): No adverse effects were seen in body weight, sex distribution, survival, or gross pathology of pups delivered.

Comments:

Reference: Schroeder, R.E. (1989). A Two-Generation Reproduction Study in Rats with Hydroquinone (Unpublished report), Eastman Kodak Internal Report TX-90-13, Bio-dynamics Inc., East Millstone, NJ.

6.7.2 **Teratogenicity/Developmental toxicity**

Test substance: Hydroquinone (99%) in distilled water

Test species/strain: Sprague-Dawley Rats

Test method (e.g., OECD, others): OECD Guideline 414. Animals treated with 0, 30, 100, or 300 mg/kg/day by gavage.

GLP: YES []
NO [

Test results: Body weights and feed consumption were significantly reduced in dams receiving 300 mg/kg. No other toxicity was observed. Reproductive indices were comparable in all groups. A few spontaneous soft-tissue and skeletal malformations were observed in all dose groups and were not considered to be treatment-related. Fetal body weights in the 300 mg/kg dose group were slightly reduced compared with the control group, but this was correlated to the reduced maternal weight gain.

NOEL for maternal animals = 100 mg/kg
NOEL for offspring = 300 mg/kg

Comments:

Reference: Krasavage, W.J., Blacker, A.M., English, J.C., and Murphy, S.J. (1992). Hydroquinone: A Developmental Toxicity Study in Rats, *Fundam. Appl. Toxicol.* 18, 370-375.

6.7.2 **Teratogenicity/Developmental toxicity** (Additional study)

Test substance: Hydroquinone (99%) in distilled water

Test species/strain:	New Zealand White Rabbits
Test method (e.g., OECD, others):	OECD Guideline 414. Animals treated with 0, 25, 75, or 150 mg/kg/day by gavage.
GLP:	YES [X] NO []
Test results:	No mortality occurred. Pregnancy rates were 15/18 in the control group, 18/18 in the low-dose group, 18/18 in the mid-dose group, and 17/18 in the high-dose group. No spontaneous abortions were observed, and the incidence of early delivery (Day 26 and Day 30) was comparable in all groups. No maternal toxicity, embryotoxicity, fetotoxicity, or teratogenicity was observed at 25 or 75 mg/kg. At 150 mg/kg, maternal toxicity was evident as lower body weight and feed consumption. No clinical signs of toxicity were noted. A few soft-tissue and skeletal abnormalities were noted in the high dose group, but these were not significantly different from the control group and were considered to reflect maternal toxicity. NOEL for maternal animals = 25 mg/kg NOEL for offspring = 75 mg/kg
Comments:	
Reference:	Murphy, S.J., Schroeder, R.E., Blacker, A.M., Krasavage, W.J., and English, J.C. (1992). A Study of Developmental Toxicity of Hydroquinone in Rabbits, <u>Fundam. Appl. Toxicol.</u> 19, 214-221.

6.8 Specific toxicities (Neurotoxicity)

Test substance:	Hydroquinone (>99%)
Test species/strain:	Sprague-Dawley rats
Test method:	According to USEPA TSCA Guideline 40 CFR 798.6050. Neurohistopathology was conducted on the forebrain, cerebrum, midbrain, cerebellum, pons, medulla oblongata, cervical spinal cord swelling, lumbar spinal cord swelling, cervical and lumbar dorsal root, dorsal-ventral spinal roots, sciatic nerve and tibial nerve. Animals received 0, 20, 64, or 200 mg/kg in distilled water by gavage for 13 weeks (5 days per week).
GLP:	YES [X] NO []

Test results: No mortality occurred. Tremors and reduced home-cage activity were observed in mid- and high-dose groups immediately after dosing with the incidence increased in a dose-dependent manner. All treated groups were noted with brown discolored urine. No differences in body weight or feed consumption were noted. No differences in brain or kidney weight were observed. No morphologic lesions associated with treatment were observed.

Comments:

Reference: Bernard, L.G. (1988). Subchronic Oral Toxicity Study of Hydroquinone in Rats Utilizing a Functional-Observational Battery and Neuropathology to Detect Neurotoxicity (Unpublished report TX-88-78), Eastman Kodak Company.

6.9 Toxicodynamics, toxico-kinetics

Test substance: Hydroquinone (97% radiochemical purity)

Test species/strain: Sprague-Dawley Rats

Test method: Male rats were divided into groups of 4 animals per group and received: ¹⁴C-Hydroquinone in a single oral dose of 5, 30, or 200 mg/kg; and 200 mg/kg unlabeled hydroquinone for 4 days by gavage followed by a single dose of 200 mg/kg dose ¹⁴C-Hydroquinone. In order to identify metabolites, animals were given hydroquinone in the the feed (5.6%) for 2 days, while other animals were given 311 mg/kg ¹⁴C-Hydroquinone by gavage. The urine from these animals was collected, pooled and analyzed for metabolites.

GLP: YES []
NO [X]

Test results: With 97-102% of the total radioactivity accounted for, the primary route of elimination is the urine (92-99%) with 87% of the total radioactivity recovered being excreted in the first 24 hours. The feces contained 2-4% of the total radioactivity recovered. Less than 1% of the dose was expired as CO₂ and less than 2% remained in the carcass after 96 hours. The dose administered did not influence the excretion pattern of radioactivity. Tissues concentrations of remaining radioactivity in the carcass were highest the liver and kidneys, with all other organs having comparable levels. The distribution did not change with repeated dosing.

Analysis of urine for metabolites indicated that 1% of the radioactivity was excreted as unchanged hydroquinone. The majority of the radioactivity was identified as a glucuronide conjugate with a smaller portion as a sulfate conjugate.

However, the relative amounts of each conjugate were different after single and repeated dosing. After repeated dosing, 72% of the radioactivity was glucuronide and 23% sulfate conjugate, while after a single dose 56% was glucuronide and 43% sulfate conjugate. No differences in the metabolite pattern was observed in animals treated by gavage or as dietary admix.

Comments: Study predates GLP regulations. Additional studies listed in the attached bibliography.

Reference: DiVincenzo, G., Hamilton, M., Reynolds, R., and Ziegler, D. (1984). Metabolic Fate and Disposition of [¹⁴C]Hydroquinone Given Orally to Sprague-Dawley Rats, *Toxicology* 33, 9-18.

6.9 Toxicodynamics, toxico-kinetics (Additional study)

Test substance: Hydroquinone (99.6%)

Test species/strain: Male Fischer 344 Rats

Test method: Groups of 4 rats per group were treated with 50 mg/kg of hydroquinone by gavage (i.g.), intravenous injection (i.v.), or intratracheal (i.t.) instillation and blood collected for up to 8 hours through an indwelling catheter. Other animals were treated and euthanatized at 10 min, 20 min, 40 min, 1 hr, 2 hr, and 4 hr after treatment and the levels of radioactivity in the tissues determined.

GLP: YES [
NO [

Test results: Absorption was rapid after i.g. administration with a $t_{1/2}$ value of approximately 1 min. Distribution of radioactivity was similar for all three routes of administration. The $\theta t_{1/2}$ was 22, 19, and 15 min for i.t., i.v., and i.g. treatment, respectively. Elimination was also rapid with $Kt_{1/2}$ values of 626, 326, and 425 min for i.t., i.v., and i.g., respectively. Radioactivity in the blood was associated initially with the plasma, but these levels decline rapidly in the first 60 min. By 4 hours, 64% of the radioactivity is associated with the red blood cells.

Analysis of plasma indicates rapid metabolism of hydroquinone. Only 1% of the total radioactivity in the plasma ultrafiltrate was unaltered hydroquinone. Glucuronide and glutathione conjugates of hydroquinone were detected 40 min after i.g. administration. A fourth material was also detected but not identified.

Comments: Additional studies listed in the attached bibliography.

Reference: Fox, J.A., English, J.C., and Lockhart, Jr., H.B. (1986). Blood Elimination Kinetics of [U-¹⁴C]Hydroquinone Administered by Intra-gastric Intubation, Intratracheal Instillation or Intravenous Injection to Male Fischer 344 Rats (Unpublished report TX-86-1), Eastman Kodak Company.

6.9 **Toxicodynamics, toxico-kinetics** (Additional study)

Test substance: Hydroquinone (99.6%)

Test species/strain: Fischer 344 Rats

Test method: OECD Guideline 417. Groups of animals received ¹⁴C-Hydroquinone in a single oral dose of 350 or 25 mg/kg; after 14 repeated doses of unlabelled 25 mg/kg/day; and as a single dermal application (24 hour occlusive exposure) of 150 or 25 mg/kg. Urine and feces were collected for 7 days and plasma concentrations determined for 96 hours. Tissue levels were determined 48 and 72 hours after the single oral dose, 48 hours the repeated doses, and 168 hours after the dermal dose.

GLP: YES [X]
NO []

Test results: After oral administration, the blood concentrations indicated rapid absorption (14-19 min after single 25 mg/kg dose; 10-14 after repeated 25 mg/kg doses; 34-48 min after single 350 mg/kg dose) followed by a biphasic elimination phase. The $t_{1/2}$ ranged from 0.2 - 1.7 hours. The $t_{1/2}$ for the low dose ranged from 2.8 - 10.5 hours and could not be estimated for the high dose. Blood concentrations after dermal application were generally below the limit of detection.

Elimination of radioactivity occurred within the first 8 hours after oral administration primarily in the urine (92-97% after a dose of 25 mg/kg, and 87% after 350 mg/kg dose). Approximately 1.3-2.0% was excreted in the feces. No differences between the excretion from males or females were observed. Less than 1% remained in the tissues. The liver and kidneys contained the highest concentrations with females generally having higher concentrations than males.

Approximately 61-71% of the dermal dose was recovered from the application site immediately after dosing. After 168 hours, the skin at the application site contained 0.14-2.2% of the total radioactivity. Only 15-18% of the total radioactivity was recovered in the urine with 1.7-3.7% in the feces. Approximately 2.6 - 12.9% of the total radioactivity was associated with the tissues and carcass.

Urinary metabolites were separated by HPLC and identified. Approximately 45-53% of the excreta from an oral dose was the glucuronide conjugate of hydroquinone, and 19-33% was the sulfate conjugate. A mercapturic acid conjugate was also identified but accounted for only 4.7% of the dose in females and 2.3% of the dose in males at 350 mg/kg. Mercapturate was occasionally detected in the urine from the 25 mg/kg group. The parent compound was less than 3% of the dose. After dermal exposure, 27-45% of the radioactivity recovered in the urine was the glucuronide conjugate with only a small fraction identified as the sulfate conjugate. The parent compound accounted for 3-8% of the recovered radioactivity. Mercapturic acid conjugates were occasionally detected in dermally-dosed animals.

Comments: Additional studies listed in the attached bibliography. Test material leaked from the application site, and oral exposure could not be ruled out.

Reference: English, J.C., Deisinger, P.J., Perry, L.G., Schum, D.B., and Guest, D. (1988). Toxicokinetics Studies with Hydroquinone in Male and Female Fischer 344 Rats (Unpublished report TX-88-84), Eastman Kodak Company.

6.9 Toxicodynamics, toxico-kinetics (Additional study)

Test substance: Hydroquinone (99%) in water

Test species/strain: male Beagle dogs

Test method: Skin on the thorax of six male dogs was shaved and 25 mL of a [¹⁴C]-hydroquinone in water solution (4.5 g/L) was added to a 15 x 4 cm absorption cell. The solution was held in contact with the skin for 60 minutes. Blood was collected 4, 8, 24, and 48 hours after application of the test substance. Urine was collected 4, 8, 24, 48, 72, 96, and 120 hours after application of the test substance. The level of radioactivity determined in blood and urine samples.

GLP: YES []
NO []

Test results: No measurable radioactivity was found in blood. Urinary excretion of radioactivity was low with the peak between 24 and 48 hours. The dermal absorption rate was calculated to be 1.1/μg/cm²hr.

Comments:

Reference: Hamilton, M.L., Guest, D., and DiVincenzo, G.D. (1985). The Percutaneous Absorption of [U-¹⁴C]Hydroquinone in

Beagle Dogs (Unpublished report TX-85-87), Eastman Kodak Company.

6.9 **Toxicodynamics, toxico-kinetics** (Additional study)

Test substance: 5% (w/v) Hydroquinone (>99%) in water

Test species/strain: Fischer 344 Rats and Human abdominal skin

Test method: Whole skin sections from the abdominal area of rats or stratum corneum of human abdominal skin were placed onto Franz-type diffusion cells. Tritiated water or [¹⁴C]-hydroquinone in water were added to donor chambers containing buffered, nutrient saline with antibiotic. Samples were withdrawn from the receptor chamber each hour for a total of eight hours and the level of radioactivity determined.

GLP: YES [X]
NO []

Test results: The permeation constant for the hydroquinone through whole rat skin was 2.26×10^{-5} cm/hr compared with a constant of 2.34×10^{-3} cm/hr for ³H₂O. Using human stratum corneum, the permeation constants were 9.33×10^{-6} cm/hr for hydroquinone and 0.97×10^{-3} cm/hr for ³H₂O. These values indicate that dermal absorption of hydroquinone is "slow" using the criteria of Marzulli *et al.* (1969).

Comments:

Reference: Barber, E.D., Hill, T., and Schum, D.B. (1993). The Absorption of Hydroquinone (HQ) through Rat and Human Skin *in vitro*. *Toxicology Letters* 80:167-172.

ADDITIONAL REFERENCES

Bolcsak, L. E., and Nerland, D. E. (1983). Inhibition of Erythropoiesis by Benzene and Benzene Metabolites. *Toxicol. Appl. Pharmacol.* 69, 363-368.

Lockhart, H. B., Fox, J. A., and DiVincenzo, G. (1984). The Metabolic Fate of [U-¹⁴C]Hydroquinone Administered by Gavage to Male Fischer 344 Rats (Unpublished report BC-84-14), Health and Environment Laboratories, Eastman Kodak Company.

Lockhart, H. B., and Fox, J. A. (1985). Metabolic Fate of [U-¹⁴C]Hydroquinone Administered by Gavage to Female Fischer 344 Rats (Unpublished report TX-85-55), Health and Environment Laboratories, Eastman Kodak Company.

Lockhart, H. B., and Fox, J. A. (1985). The Metabolic Fate of [U-¹⁴C]Hydroquinone Administered by Intratracheal Instillation to Male Fischer 344 Rats (Unpublished report TX-85-76), Health and Environment Laboratories, Eastman Kodak Company.

7. **Experience with Human Exposure (give full description of study design, effects of Accidental or Occupational Exposure, epidemiology)**

A study of the levels of hydroquinone ingested from natural sources was conducted in human volunteers. A group of two nonsmoking males and two nonsmoking females were given diets that consisted of low and high levels of hydroquinone. A group of smokers (two males and two females) received only the low-hydroquinone diet followed by smoking four cigarettes in 20 minutes. Blood samples were collected and analyzed at 30, 60, and 120 minutes after eating or immediately, 30, and 90 minutes after smoking. Plasma levels of hydroquinone following the high-HQ diet increased five fold above background, while plasma levels decreased after a low-HQ diet. Plasma levels of hydroquinone increased by 50% immediately after smoke and declined to near background levels by 90 minutes. Urine was collected for up to 8 hours. Rates of urinary excretion of hydroquinone reflect plasma levels.

Reference: Deisinger, P.J., Hill, T.S., and English, J.C. (1994). Human Exposure to Naturally Occurring Hydroquinone, The Toxicologist 14, 788.

Two male volunteers ingested 500 mg of hydroquinone daily for 5 months. Doses were divided into thirds and given with meals. Blood samples were analyzed for hemoglobin concentration, hematocrit, red blood cell count, differential white blood cell count, sedimentation rate, platelet count, coagulation time, and icteric index. Urine was analyzed for albumin, reducing sugars, blood cells, casts, and urobilinogen. No abnormal findings were reported in blood or urine.

Reference: Carlson, A.J., and Brewer, N.R. (1953). Toxicity Studies on Hydroquinone, Proc. Soc. Exper. Biol. Med. 84, 684-688.

Seventeen male and female volunteers ingested 300 mg of hydroquinone daily for 3-5 months. Doses were divided into thirds and given with meals. Blood samples were analyzed for hemoglobin concentration, hematocrit, red blood cell count, differential white blood cell count, sedimentation rate, platelet count, coagulation time, and icteric index. Urine was analyzed for albumin, reducing sugars, blood cells, casta, and urobilinogen. No abnormal findings were reported in blood or urine.

Reference: Carlson, A.J., and Brewer, N.R. (1953). Toxicity Studies on Hydroquinone, Proc. Soc. Exper. Biol. Med. 84, 684-688.

7.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A retrospective study was conducted in which 50 cases of eye injury in workers involved in the manufacture of hydroquinone were evaluated. Workmen exposed to vapors of quinone and dust of hydroquinone developed reversible discoloration of the cornea and interpalpebral fissure, or frank corneal opacity. These lesions developed slowly and were not evident in workers that were exposed for less than five years. Hematology from these workers, and from all workers exposed to hydroquinone, were evaluated over a two year period with no systemic effects indicated.

Reference: Sterner, J.H., Oglesby, F.L., and Anderson, B. (1947). Quinone Vapors and Their Harmful Effects, J. Ind. Hyg. Toxicol. 29, 60-73.

Another study in which 31 employees involved in the packaging of photochemicals (including hydroquinone) were evaluated for eye injury. The group consisted of 15 males with 6 months to 24 years of exposure, and 12 females with 8 to 18 years of exposure. Four additional males who had exposure for 2-6 years were also included. No ocular lesions attributable to hydroquinone were noted.

Reference: Sutton, W.L. (1961). Internal memo, Laboratory of Industrial Medicine, Eastman Kodak Company.

An increase in the prevalence of coughing in response to a "smoky environment", increased immunoglobulin G, and lower respiratory function values (FEV) were noted in 33 workers exposed to a combination of hydroquinone, trimethylhydroquinone, and retinene-hydroquinone compared to a control group from the same plant. Duration of employment, age, and the percentage of smokers were matched. No airborne concentrations of hydroquinone are provided and there was no indication of the duration of exposure to hydroquinone versus other chemicals.

Reference: Choudat, D., Neukirch, F., Brochard, P., Barrat, G., Marsac, J., Conso, F., and Philbert, M. (1988). Allergy and Occupational Exposure to Hydroquinone and to Methionine, Br. J. Ind. Med. 45, 376-380.

A single case of vitiligo and lichenoid eruption was reported in a individual who serviced automatic self-photography machines which contained a developer that used 7% hydroquinone. The individual did demonstrate sensitization to a color developer.

Reference: Kersey, P., and Stevenson, C.J. (1981). Vitiligo and Occupational Exposure to Hydroquinone from Servicing Self-Photography Machines, Contact Derm. 7, 285-287.

A single case of vitiligo was reported in a dark-skinned West African man who had immersed his hand into a commercial black-and-white developer containing 0.06% hydroquinone.

Reference: Frenk, E., and Loi-Zedda, P. (1981). Occupational Depigmentation Due to a Hydroquinone-containing Photographic Developer, Contact Derm. 6, 238-239.

A cohort study of 478 photographic processors in nine Eastman Kodak Color Print and Processing laboratories reported no significant excess mortality, sickness-absence, or cancer incidence. The mortality experience compared favorably with two control industrial populations.

Reference: Friedlander, B.R., Hearne, F.T., and Newman, B.J. (1982). Mortality, Cancer Incidence, and Sickness-Absence in Photographic Processors: An Epidemiological Study, J. Occup. Med. 24, 605-613.

A cohort study of 9,040 men employed at Eastman Chemical Co. in Tennessee reported significantly decreased mortality and diseases of the circulatory system compared with the general population in Tennessee. Among the chemicals that some of these individuals were exposed to is hydroquinone, although it was not the only source of exposure.

Reference: Pifer, J.W., Hearne, F.T., Friedlander, B.R., and McDonough, J.R. (1986). Mortality Study of Men Employed at a Large Chemical Plant, 1972 Through 1982, *J. Occup. Med.* 28, 438-444.

A study of 78 photographic processors in the Sweden Television Film Laboratory was conducted in which individuals who were patch tested for sensitization to chemicals used in the workplace were monitored for occupation-related illness. The Laboratory had undergone modernization which reduced the potential exposure of these workers and the investigators monitored the workers to determine if the modernization was effective in reducing occupation-related problems. The study showed that occupation-related illness and leave was reduced to an incidence of zero. No contact dermatitis or other skin disorder was noted after modernization compared with 37 cases prior to modernization.

Reference: Lidén, C. (1989). Occupational Dermatoses at a Film Laboratory, *Contact Dermat* 20, 191-200.

A cohort study of 858 men and 21 women involved in the manufacture and use of hydroquinone was conducted to evaluate total mortality and cancer-related deaths. Individuals worked for a mean of 13.7 years in jobs that involved the manufacture or use of hydroquinone. No increase in the incidence of renal cancer was detected in the study population, and no deaths from liver cancer or leukemia occurred. The incidences of other pathological conditions such as respiratory malignancies, cardiovascular disease, and digestive disease were below expected levels.

Reference: Pifer, J.W., Hearne, F.T., Swanson, F.A., O'Donoghue, J.L. (1995). Mortality Study of Employees Engaged in the Manufacture and Use of Hydroquinone, *Int. Arch. Occup. Environ. Health* 67:267-280.

8. **Recommended Precautions, Classification (use and/or transportation) and Safety Data Sheets.**

9. **Availability and reference(s) for existing review(s)**

International Programme on Chemical Safety (IPCS), Environmental Health Criteria 157: Hydroquinone. World Health Organization, 1994.

10. **Name of responder**

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Corporate Health and Environment Laboratories
Eastman Kodak Company
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Fax: (716) 722-7561

APPENDIX OF REPORTS REFERENCED IN THE DOSSIER BUT NOT CITED IN THE LITERATURE

The following lists the reports in this Appendix.

1. Dagon, T.J. (1975). Aquatic Toxicity Report (Unpublished report), Health and Safety Laboratory, Eastman Kodak Company.
2. Dagon, T.J. (1975). Vascular Phytotoxicity Report (Unpublished report), Health and Safety Laboratory, Eastman Kodak Company.
3. Hodge, H.C., Maynard, E.A., Wilt, Jr., W.G., and Kesel, R. (1949). Studies of the Acute Toxicity of Hydroquinone (Unpublished report), Division of Pharmacology and Toxicology, University of Rochester School of Medicine and Dentistry.
4. Toxicity Report (Unpublished report), Laboratory of Industrial Medicine, Eastman Kodak Company, 1971.
5. Bernard, L.G. (1988). Subchronic Oral Toxicity Study of Hydroquinone in Rats Utilizing a Functional-Observational Battery and Neuropathology to Detect Neurotoxicity (Unpublished report TX-88-78), Eastman Kodak Company.
6. David, R. (1994). NDMA High HQ Formulation Cream: A Thirteen-Week Dermal Toxicity and Cell Proliferation Study in the Rat (unpublished report), Nonprescription Drug Manufacturers Association.
7. Hamilton, M.L., Guest, D., and DiVincenzo, G.D. (1985). The Percutaneous Absorption of [U - ¹⁴C]Hydroquinone in Beagle Dogs (Unpublished report TX-85-87), Eastman Kodak Company.
8. Schroeder, R.E. (1989). A Two-Generation Reproduction Study in Rats with Hydroquinone (Unpublished report), Eastman Kodak Internal Report TX-90-13, Bio-dynamics Inc., East Millstone, NJ.
9. Fox, J.A., English, J.C., and Lockhart, Jr., H.B. (1986). Blood Elimination Kinetics of [U - ¹⁴C]Hydroquinone Administered by Intragastric Intubation, Intratracheal Instillation or Intravenous Injection to Male Fischer 344 Rats (Unpublished report TX-86-1), Eastman Kodak Company.
10. English, J.C., Deisinger, P.J., Perry, L.G., Schum, D.B., and Guest, D. (1988). Toxicokinetics Studies with Hydroquinone in Male and Female Fischer 344 Rats (Unpublished report TX-88-84), Eastman Kodak Company.

EXTRACT FROM IRPTC LEGAL FILES

file: 17.01 LEGAL rn : 100268
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : ARG type : REG

subject	specification	descriptor
AIR	OCC	MPC

8H-TWA : 2 MG/M3

entry date: OCT 1991

effective date: 29MAY1991

title: LIMIT VALUES FOR CHEMICAL SUBSTANCES IN THE WORKING ENVIRONMENT-RESOLUTION NO. 444/1991 OF THE MINISTRY OF WORK AND SOCIAL SECURITY (AMENDING REGULATION DECREE NO. 351/1979 UNDER LAW NO. 19587/1972: HYGIENE AND SAFETY AT WORK)
 original : ARGOB*, BOLETIN OFICIAL DE LA REPUBLICA ARGENTINA(ARGENTIAN OFFICIAL BULLETIN), 24170 , I , 1 , 1979
 amendment: ARGOB*, BOLETIN OFICIAL DE LA REPUBLICA ARGENTINA(ARGENTIAN OFFICIAL BULLETIN), 27145 , I , 4 , 1991

file: 17.01 LEGAL rn : 300104
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : CAN type : REG

subject	specification	descriptor
AIR	OCC	TLV

TWA: 2 mg/m3. Prescribed by the Canada Occupational Safety and Health Regulations, under the Canada Labour Code (administered by the Department of Employment and Immigration). The regulations state that no employee shall be exposed to a concentration of an airborne chemical agent in excess of the value for that chemical agent adopted by ACGIH (American Conference of Governmental Industrial Hygienists) in its publication entitled: "Threshold Limit Value and Biological Exposure Indices for 1985-86". The regulations also state that the employer shall, where a person is about to enter a confined space, appoint a qualified person to verify by means of tests that the concentration of any chemical agent or combination of chemical agents will not result in the exposure of the person to a concentration in excess of the value indicated above. These regulations prescribe standards whose enforcement will provide a safe and healthy workplace.
 entry date: OCT 1994 effective date: 24MCH1994

amendment: CAGAAK, CANADA GAZETTE PART II, 128 , 7 , 1513 , 1994

file: 17.01 LEGAL rn : 301985
 systematic name:1,4-Benzenediol

common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : CAN type : REG

subject	specification	descriptor
TRNSP		CLASS
LABEL		RQR
PACK		

Schedule II, List II - Dangerous Goods other than Explosives: PIN
 (Product Identification No.): UN2662. Class (6.1): Poisonous. Packing
 group III, (I=Great danger, III=Minor danger). Passenger Vehicles: 100
 kg. Prescribed by the Transportation of Dangerous Goods Regulations,
 under the Transportation of Dangerous Goods Act (administered by the
 Department of Transport). The act and regulations are intended to
 promote safety in the transportation of dangerous goods in Canada, as
 well as provide comprehensive regulations applicable to all modes of
 transport across Canada. These are based on United Nations
 recommendations. The act and regulations should be consulted for
 details. Information is entered under the proper shipping name found in
 the regulations; this may include general groups of chemical substances.
 entry date: OCT 1994 effective date: 02DEC1993

amendment: CAGAAK, CANADA GAZETTE PART II, 127 , 25 , 4056 , 1993

file: 17.01 LEGAL rn : 303138
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : CAN type : REG

subject	specification	descriptor
USE	OCC	RQR
STORE		
LABEL		

Ingredient Disclosure List - Concentration: 1% weight/weight. The
 Workplace Hazardous Materials Information System (WHMIS) is a national
 system providing information on hazardous materials used in the
 workplace. WHMIS is implemented by the Hazardous Products Act and the
 Controlled Products Regulations (administered by the Department of
 Consumer and Corporate Affairs). The regulations impose standards on
 employers for the use, storage and handling of controlled products. The
 regulations also address labelling and identification, employee
 instruction and training, as well as the upkeep of a Materials Safety
 Data Sheet (MSDS). The presence in a controlled product of an ingredient
 in a concentration equal to or greater than specified in the Ingredient
 Disclosure List must be disclosed in the Safety Data Sheet.
 entry date: APR 1991 effective date: 31DEC1987

amendment: CAGAAK, CANADA GAZETTE PART II, 122 , 2 , 551 , 1988

file: 17.01 LEGAL rn : 401860
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : CSK type : REG

subject	specification	descriptor
GOODS		PRO

PROHIBITED IN COSMETICS

entry date: DEC 1991

effective date: 1JAN1971

title: DIRECTIVE NO. 34 ON HYGIENIC REQUIREMENTS ON COSMETICS,
 DETERGENTS, AND GOODS OF PERSONAL USE

original : HPMZC*, HYGIENICKE PREDPISY MINISTERSTVA ZDRAVOTNICTVI
 CSR(HYGIENIC REGULATIONS OF MINISTRY OF HEALTH OF CSR), 32 ,
 , , 1970

file: 17.01 LEGAL rn : 523103
 !!! WARNING - not original IRPTC record - WARNING !!!
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : DEU type : REG

subject	specification	descriptor
AQ		CLASS
USE	INDST	RQR

This substance is classified as hazardous to water (Water Hazard Class: WHC 2). (There are 3 water hazard classes: WHC 3 = severely hazardous; WHC 2 = hazardous; WHC 1 = moderately hazardous; and the classification as "not hazardous to water"). The purpose of the classification is to identify the technical requirements of industrial plants which handle substances hazardous to water.

entry date: SEP 2001

effective date: 01JUN1999

title: Administrative Order relating to Substances Hazardous to Water
 (Verwaltungsvorschrift wassergefaehrdende Stoffe)

original : BUANZ*, Bundesanzeiger, 51 , 98a , 1 , 1999

file: 17.01 LEGAL rn : 540458
 !!! WARNING - not original IRPTC record - WARNING !!!
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000

area : DEU type : REC

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|subject|specification|descriptor|
|-----+-----+-----|
| AIR   | OCC       | MAK   |
|-----+-----+-----|

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No MAK value established. - Carcinogen category 2: Substance that is considered to be carcinogenic for man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that it can make a significant contribution to cancer risk. Limited data from animal studies can be supported by evidence that the substance causes cancer by a mode of action that is relevant to man and by results of in vitro tests and short-term animal studies. - Germ cell mutagen category 3 (old classification): Substance which has been demonstrated to cause genetic damage in mammalian (including human) germ cells without proof of transmission. Classification in one of the new categories is in progress.

entry date: MAY 2001

title: List of MAK and BAT Values 2000. Maximum Concentrations and Biological Tolerance Values at the Workplace. (MAK- und BAT-Werte-Liste 2000. Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte.)

original : MPGDFD, Mitteilung der Senatskommission zur Pruefung gesundheitsschaedlicher Arbeitsstoffe, 36 , , , 2000

file: 17.01 LEGAL rn : 600172
systematic name:1,4-Benzenediol
common name :p-Hydroquinone
reported name :Quinol
cas no :123-31-9 rtecs no :MX3500000
area : GBR type : REC

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|subject|specification|descriptor|
|-----+-----+-----|
| AQ    | METHD     | RQR    |
|       | DRINK     |        |
|-----+-----+-----|

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Determines this substance in rivers, waters, sewage effluents and industrial effluents using the trimethyl-silylethers and gas chromatography.

entry date: MCH 1995

effective date: 1981

title: Phenols in Waters and Effluents by Gas Liquid Chromatography or 3-Methyl-2-benzothiazoline Hydrazone.

original : SCAA**, , , , , 1983

file: 17.01 LEGAL rn : 700694
systematic name:1,4-Benzenediol
common name :p-Hydroquinone
reported name :Hydroquinone
cas no :123-31-9 rtecs no :MX3500000
area : IND type : REG

subject	specification	descriptor
MANUF		RQR
SAFTY		RQR
STORE		RQR
IMPRT		RQR

These rules define the responsibilities of occupiers of any industrial activity in which this toxic and hazardous substance may be involved. These responsibilities encompass: (a) assessment of major hazards (causes, occurrence, frequency); (b) measures to prevent accidents and limit eventual impairment to human health and pollution of the environment; (c) provision of relevant factual knowledge and skills to workers in order to ensure health and environmental safety when handling equipments and the foregoing chemical; (d) notification of the competent authorities in case of major accidents; (e) notification of sites to the competent authorities 3 months before commencing; (f) preparation of an on-site emergency plan as to how major accidents should be coped with; (g) provision of competent authorities with information and means to respond quickly and efficiently to any off-site emergency; (h) provision of information to persons outside the site, liable to be affected by a major accident; (i) labelling of containers as to clearly identify contents, manufacturers, physical, chemical and toxicological data; (j) preparation of a safety data sheet including any significant information regarding hazard of this substance and submission of safety reports to the competent authorities; (k) for the import of a hazardous chemical to India, importers must supply the competent authorities with specified information regarding the shipment.

entry date: SEP 1992

effective date: 27NOV1989

title: THE MANUFACTURE, STORAGE AND IMPORT OF HAZARDOUS CHEMICALS RULES. 1989

original : GAZIN*, THE GAZETTE OF INDIA, 787 , , , 1989

file: 17.01 LEGAL rn : 1010157

systematic name: 1,4-Benzenediol

common name : p-Hydroquinone

reported name : DIHYDROXYBENZENE

cas no : 123-31-9

rtcs no : MX3500000

area : MEX

type : REG

subject	specification	descriptor
AIR	OCC	MXL

AT ANY WORKPLACE WHERE THIS SUBSTANCE IS PRODUCED, STORED OR HANDLED A MAXIMUM PERMISSIBLE LEVEL OF 2MG/M3 MUST BE OBSERVED FOR A PERIOD OF 8 HOURS.

entry date: DEC 1991

effective date: 28MAY1984

title: INSTRUCTION NO.10 RELATED TO SECURITY AND HYGIENIC CONDITIONS AT WORKPLACES. (INSTRUCTIVO NO. 10, RELATIVO A LAS CONDICIONES DE SEGURIDAD E HIGIENE DE LOS CENTROS DE TRABAJO).

original : DOMEX*, DIARIO OFICIAL, , , , 1984

file: 17.01 LEGAL rn : 1105209
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : RUS type : REG

subject	specification	descriptor
AQ	SURF	MAC CLASS

0.2 MG/L HAZARD CLASS: IV
 entry date: JUL 1990 effective date: 1JAN1989

amendment: SPNPV*, SANITARNYE PRAVILA I NORMY OKHRANY POVERKHNOSTNYKH
 VOD OT ZAGRIAZNENIA (HEALTH REGULATION AND STANDARDS OF
 SURFACE WATER PROTECTION FROM CONTAMINATION), 4630-88 , , ,
 1988

file: 17.01 LEGAL rn : 1111547
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : RUS type : REG

subject	specification	descriptor
AIR	OCC	MAC CLASS

CLV: 1.0MG/M3 (AEROSOL) HAZ. CLASS: II
 entry date: MAY 1990 effective date: NOV1989

amendment: PDKAD*, PREDELNO DOPUSTIMYE KONTSENTRATSII VREDNYKH
 VESHCHESTV V VOZDUKHERABOCHEI ZONY (MAXIMUM ALLOWABLE
 CONCENTRATIONS OF HARMFUL SUBSTANCES IN OCCUPATIONAL AIR),
 5147-89 , , , 1989

file: 17.01 LEGAL rn : 1121881
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : RUS type : REG

subject	specification	descriptor
AIR	AMBI	PSL

0.02MG/M3 1X/D

entry date: SEP 1985

effective date: DEC1983

amendment: OBUAV*, ORIENTIROVOCHNYE BEZOPASNYE UROVNI VOZDEISTVIA (OBUV)
 ZAGRAZNIAIUSHCHIKH VESHCHESTU V ATMOSFERNOM VOZDUKHE
 NASEKENNYKH MEST (TENTATIVE SAFE EXPOSURE LIMITS (TSEL) OF
 CONTAMINANTS IN AMBIENTAIR OF RESIDENTIAL AREAS), 2947-83 , ,
 , 1983

file: 17.01 LEGAL rn : 1200045

systematic name:1,4-Benzenediol

common name :p-Hydroquinone

reported name :Hydroquinone

cas no :123-31-9

rtecs no :MX3500000

area : SWE

type : REG

subject	specification	descriptor
AIR	OCC	HLV

1D-TWA: 0.5MG/M3; 15MIN-STEL: 1.5MG/M3. SENSITIZING.

entry date: 1992

effective date: 01JUL1991

title: HYGIENIC LIMIT VALUES.

original : AFS***, ARBETARSKYDDSSSTYRELSENS FOERFATTNINGSSAMLING, 1990:13
 , , 5-64 , 1990

file: 17.01 LEGAL rn : 1301168

systematic name:1,4-Benzenediol

common name :p-Hydroquinone

reported name :Hydroquinone

cas no :123-31-9

rtecs no :MX3500000

area : USA

type : REG

subject	specification	descriptor
MANUF	REQ	PRMT
USE	OCC	PRMT
SAFTY	OCC	MXL

; Summary - THE FOLLOWING CHEMICAL IS INCLUDED ON A LIST OF CHEMICALS
 AND MIXTURES FOR WHICH REPORTING IS CURRENTLY REQUIRED UNDER THE TOXIC
 SUBSTANCES CONTROL ACT SECTION 2607A. THIS TOXIC SUBSTANCE IS SUBJECT TO
 PRELIMINARY ASSESSMENT INFORMATION RULES ON PRODUCT ION QUANTITIES,
 USES, EXPOSURES, AND ADVERSE EFFECTS. MANUFACTURERS INCLUDING IMPORTERS
 MUST SUBMIT A REPORT FOR THIS LISTED CHEMICAL MANUFACTURED AT EACH SITE.
 entry date: OCT 1991 effective date: 1982

title: PRELIMINARY ASSESSMENT INFORMATION RULES

original : FEREAC, FEDERAL REGISTER, 47 , , 26998 , 1982

amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 712 , 30 , 1990

file: 17.01 LEGAL rn : 1307147
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : USA type : REG

subject	specification	descriptor
AIR	EMI	RQR

; Summary - FROM A LIST OF POLLUTANTS JUDGED TO BE HAZARDOUS FOR WHICH
 EMISSION STANDARDS WILL BE DEVELOPED
 entry date: SEP 1991 effective date: 1985

title: CLEAN AIR ACT, 112--NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR
 POLLUTANTS
 original : FERECAC, FEDERAL REGISTER, 50 , , 46290 , 1985
 amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 61 , 1 , 1990

file: 17.01 LEGAL rn : 1325189
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : USA type : REC

subject	specification	descriptor
SAFTY	OCC	MXL
USE	OCC	MXL

200 MG/M3
 entry date: OCT 1991 effective date: JUN1990

title: POCKET GUIDE TO CHEMICAL HAZARDS
 original : XPHPAW, US PUBLIC HEALTH SERVICE PUBLICATION, 90 , 117 , 128
 , 1990
 amendment: XPHPAW, US PUBLIC HEALTH SERVICE PUBLICATION, 90 , 117 , 128
 , 1990

file: 17.01 LEGAL rn : 1335161
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : USA type : REG

subject	specification	descriptor
SAFTY	INDST	RQR
STORE	INDST	RQR

TPQ=500/10,000 RQ=1; Summary - THE PRESENCE OF EXTREMELY HAZARDOUS

SUBSTANCES IN EXCESS OF THE THRESHOLD PLANNING QUANTITY (TPQ), IN POUNDS, REQUIRES CERTAIN EMERGENCY PLANNING ACTIVITIES TO BE CONDUCTED. FOR CHEMICALS THAT ARE SOLIDS, THERE MAY BE TWO TPQ'S GIVEN. IN THESE CASES, THE LOWER QUANTITY APPLIES FOR SOLIDS IN POWDER FORM WITH PARTICLE SIZE LESS THAN 100 MICRONS, OR IF THE SUBSTANCE IS IN SOLUTION OR IN MOLTEN FORM. OTHERWISE, THE HIGHER QUANTITY APPLIES. THESE CHEMICALS ARE ALSO SUBJECT TO REGULATION UNDER SARA 304. RELEASES OF SUBSTANCES, IN QUANTITIES EQUAL TO OR GREATER THAN THEIR REPORTABLE QUANTITY (RQ), IN POUNDS, ARE SUBJECT TO REPORTING TO THE NATIONAL RESPONSE CENTER UNDER THE COMPREHENSIVE ENVIRONMENTAL RESPONSE, COMPENSATION, AND LIABILITY ACT OF 1980.

entry date: OCT 1991

effective date: 1987

title: SARA, SECTION 302(A) EMERGENCY PLANNING AND COMMUNITY RIGHT TO KNOW ACT; LIST OF EXTREMELY HAZARDOUS SUBSTANCES AND THEIR THRESHOLD PLANNING QUANTITIES

original : FEREAC, FEDERAL REGISTER, 52 , , 13395 , 1987

amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 355 , , 1990

file: 17.01 LEGAL rn : 1336202

systematic name:1,4-Benzenediol

common name :p-Hydroquinone

reported name :Hydroquinone

cas no :123-31-9

rtecs no :MX3500000

area : USA

type : REG

subject	specification	descriptor
AIR	EMI	RQR
SOIL	EMI	RQR
AQ	EMI	RQR
MANUF	EMI	RQR

; Summary - FACILITIES THAT EXCEEDED A MANUFACTURING, IMPORTATION, OR PROCESSING THRESHOLD OF 25,000 LBS OR THE USE OF 10,000 LBS FOR THIS CHEMICAL MUST REPORT TO EPA ANY RELEASES OF THE CHEMICAL (OR CATEGORY CHEMICAL) TO AIR, LAND, WATER, POTW, UNDERGROUND INJECTION, OR OFF SITE TRANSFER. THIS REGULATION COVERS STANDARD INDUSTRIAL CLASSIFICATION (SIC) CODES 20-39 ONLY).

entry date: OCT 1991

effective date: 1987

title: SUPERFUND AMENDMENTS AND REAUTHORIZATION ACT, TITLE III. EPCRA SECTION 313 LIST OF TOXIC SUBSTANCES

original : CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 372 , 65 , 1988

amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 372 , 65 , 1988

file: 17.01 LEGAL rn : 1340208

systematic name:1,4-Benzenediol

common name :p-Hydroquinone

reported name :Hydroquinone

cas no :123-31-9

rtecs no :MX3500000

area : USA

type : REC

subject	specification	descriptor
AIR	OCC	TLV

Time Weighted Avg (TWA) 2 MG/M3; Summary - THIS THRESHOLD LIMIT VALUE IS INTENDED FOR USE IN THE PRACTICE OF INDUSTRIAL HYGIENE AS A GUIDELINE OR RECOMMENDATION IN THE CONTROL OF POTENTIAL HEALTH HAZARDS.
 entry date: DEC 1991 effective date: 1989

title: THRESHOLD LIMIT VALUES
 original : ACGIH*, AMERICAN CONFERENCE OF GOVERNMENT INDUSTRIAL HYGIENISTS, , , 11 , 1989
 amendment: ACGIH*, AMERICAN CONFERENCE OF GOVERNMENT INDUSTRIAL HYGIENISTS, , , 11 , 1991

file: 17.01 LEGAL rn : 1345144
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : USA type : REG

subject	specification	descriptor
MONIT		RQR

; Summary - THIS IS A CHEMICAL OR MIXTURE FOR WHICH REPORTING IS CURRENTLY REQUIRED UNDER THE TOXIC SUBSTANCE CONTROL ACT HEALTH AND SAFETY STUDIES SECTION 2607D. PERSONS WHO CURRENTLY MANUFACTURE OR PROCESS CHEMICAL SUBSTANCES OR MIXTURES FOR COMMERCIAL PURPOSES, THOSE WHO PROPOSE TO DO SO, AND THOSE WHO ARE NOT CURRENTLY INVOLVED WITH A LISTED CHEMICAL BUT WHO MANUFACTURED OR PROCESSED IT OR PROPOSED TO DO SO ANY TIME DURING THE TEN YEAR PERIOD PRIOR TO THE TIME IT BECAME LISTED MUST SUBMIT TO THE ADMINISTRATOR OF THE U.S. EPA STUDIES OR LISTS OF HEALTH AND SAFETY STUDIES CONDUCTED ON THIS SUBSTANCE FOR EVALUATION.
 entry date: OCT 1991 effective date: 1986

title: HEALTH AND SAFETY DATA REPORTING RULES SECTION 8(D)
 original : FERECAC, FEDERAL REGISTER, 51 , , 32726 , 1986
 amendment: CFRUS*, CODE OF FEDERAL REGULATIONS, 40 , 716 , 120 , 1990

file: 17.01 LEGAL rn : 1407770
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : EEC type : REG

subject	specification	descriptor
GOODS	CSMET	RSTR
GOODS	CSMET	MXL
GOODS	CSMET	RQR

THE SUBSTANCE WHICH COSMETIC PRODUCTS MUST NOT CONTAIN EXCEPT SUBJECT TO THE FOLLOWING RESTRICTIONS AND CONDITIONS: FIELD OF APPLICATION: A) OXIDIZING COLOURING AGENT FOR HAIR-DYEING: MXL = 2%; B) AGENTS FOR LOCALIZED SKIN LIGHTENER: MXL = 2%. THE SUBSTANCE MAY BE USED SINGLY OR IN COMBINATION PROVIDED THAT THE SUM OF THE RATIOS OF THE LEVELS OF EACH OF THEM IN THE COSMETIC PRODUCT EXPRESSED WITH REFERENCE TO THE MXL AUTHORIZED FOR EACH OF THEM DOES NOT EXCEED 2. WARNING WHICH MUST BE PRINTED ON THE LABEL IS GIVEN. MEMBER STATES SHALL TAKE ALL MEASURES NECESSARY TO ENSURE THAT THE COSMETIC PRODUCTS MAY BE MARKETED ONLY IF THEIR PACKAGING, CONTAINERS OR LABELS BEAR THE INFORMATION LAID DOWN.
 entry date: SEP 1995 effective date: 27MCH1978

title: COUNCIL DIRECTIVE OF 27 JULY 1976 ON THE APPROXIMATION OF THE LAWS OF THE MEMBER STATES RELATING TO COSMETIC PRODUCTS (76/768/EEC)
 original : OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L262 ,
 , 169 , 1976
 amendment: OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L181 ,
 , 31 , 1994

file: 17.01 LEGAL rn : 1408194
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :1,4-BENZENEDIOL
 cas no :123-31-9 rtecs no :MX3500000
 area : EEC type : REG

subject	specification	descriptor
GOODS	CSMET	RQR
GOODS	METHD	RQR

THE OFFICIAL METHOD FOR IDENTIFICATION AND SEMI-QUANTITATIVE DETERMINATION OF THE SUBSTANCE IN HAIR DYES IS LAID DOWN. THE SUBSTANCE IS EXTRACTED AT PH 10 WITH 96% ETHANOL FROM DYES AND IDENTIFIED BY THIN-LAYER CHROMATOGRAPHY, EITHER ONE- OR TWO-DIMENSIONAL. FOR SEMI-QUANTITATIVE DETERMINATION OF THE SUBSTANCE , THE CHROMATOGRAM OF THE SAMPLE IS COMPARED BY MEANS OF FOUR DEVELOPING SYSTEMS WITH THOSE FOR REFERENCE SUBSTANCES PRODUCED AT THE SAME TIME AND UNDER AS SIMILAR CONDITIONS AS POSSIBLE.
 entry date: SEP 1995 effective date: 31DEC1983

title: SECOND COMMISSION DIRECTIVE OF 14 MAY 1982 ON THE APPROXIMATION OF THE LAWS OF THE MEMBER STATES RELATING TO METHODS OF ANALYSIS NECESSARY FOR CHECKING THE COMPOSITION OF COSMETIC PRODUCTS (82/434/EEC)
 original : OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L185 ,
 , 1 , 1982

file: 17.01 LEGAL rn : 1408371
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :1,4-Dihydroxybenzene
 cas no :123-31-9 rtecs no :MX3500000
 area : EEC type : REG

subject	specification	descriptor
FOOD		RQR
GOODS		MXL
GOODS		PRMT

THE SUBSTANCE IS INCLUDED IN THE LIST OF AUTHORIZED MONOMERS AND OTHER STARTING SUBSTANCES, WHICH SHALL BE USED FOR THE MANUFACTURE OF PLASTICS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS. THE USE OF THE SUBSTANCE IS SUBJECT TO THE RESTRICTIONS SPECIFIED THEREIN. SPECIFIC MIGRATION LIMIT: 0.6 MG/KG. VERIFICATION OF COMPLIANCE WITH THE MIGRATION LIMITS SHALL BE CARRIED OUT IN ACCORDANCE WITH DIRECTIVES 82/711/EEC AND 85/572/EEC.

entry date: SEP 1995

effective date: 01JAN1991

title: COMMISSION DIRECTIVE OF 23 FEBRUARY 1990 RELATING TO PLASTICS MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS (90/128/EEC)

original : OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L75 , ,
19 , 1990

amendment: OJEC**, OFFICIAL JOURNAL OF THE EUROPEAN COMMUNITIES, L90 , ,
26 , 1993

file: 17.01 LEGAL rn : 1470517

!!! WARNING - not original IRPTC record - WARNING !!!

systematic name:1,4-Benzenediol

common name :p-Hydroquinone

reported name :Hydroquinone

cas no :123-31-9

rtecs no :MX3500000

area : EEC

type : REG

subject	specification	descriptor
MANUF	INDST	CLASS
IMPRT	INDST	CLASS

The substance is included in a list of existing substances produced or imported within the Community in quantities exceeding 1000 tonnes per year. - A system of data reporting by any manufacturer who has produced or any importer who has imported the substance, as such or in a preparation, in quantities exceeding 10 tonnes per year is established.

entry date: AUG 1999

effective date: 04JUN1993

title: Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances

original : OJECFC, Official Journal of the European Communities, L84 , ,
1 , 1993

file: 17.01 LEGAL rn : 1478780

!!! WARNING - not original IRPTC record - WARNING !!!

systematic name:1,4-Benzenediol

common name :p-Hydroquinone

reported name :1,4-Dihydroxybenzene

cas no :123-31-9 rtecs no :MX3500000
 area : EEC type : REG

subject	specification	descriptor
CLASS		CLASS
LABEL		RQR
PACK		RQR

Classification: Carcinogen Category 3; R40. Mutagen category 3; R40. Xn; R22. Xi: Irritant; R41. R43. N; R50. - Labelling: Xn: Harmful; N: Dangerous for the environment. Risk phrases (R): 22-40-41-43-50. Harmful if swallowed (R22). - Limited evidence of a carcinogenic effect (R40). - Risk of serious damage to eyes (R41). - May cause sensitization by skin contact (R43). - Very toxic to aquatic organisms (R50). Safety advice phrases (S): (2-)26-36/37/39-61. (Keep out of the reach of children (S2).) - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice (S26). - Wear suitable protective clothing, gloves and eye/face protection (S36/37/39). - Avoid release to the environment. Refer to special instructions/safety data sheets (S61).
 entry date: FEB 2002 effective date: 24AUG2001

title: Council Directive of 27 June 1967 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (67/548/EEC)

original : OJECFC, Official Journal of the European Communities, 196 , ,
 1 , 1967

amendment: OJECFC, Official Journal of the European Communities, L225 ,
 , 1 , 2001

file: 17.01 LEGAL rn : 1662296

!!! WARNING - not original IRPTC record - WARNING !!!

systematic name:1,4-Benzenediol

common name :p-Hydroquinone

reported name :Hydroquinone

cas no :123-31-9

rtecs no :MX3500000

area : IMO

type : REC

subject	specification	descriptor
TRNSP	MARIN	CLASS
LABEL		RQR
PACK		RQR

UN No. 2662. Class: 6.1 = Toxic substance. Packing group: III = Low danger. Applies to Hydroquinone solution and to solid Hydroquinone.

entry date: NOV 2000

effective date: 01JAN2001

title: IMDG Code - Dangerous Goods List

original : IMDGC*, International Maritime Dangerous Goods Code,
 Amendment 30-00, Volume 2 , , , 2000

file: 17.01 LEGAL rn : 1761296

!!! WARNING - not original IRPTC record - WARNING !!!
 systematic name:1,4-Benzenediol
 common name :p-Hydroquinone
 reported name :Hydroquinone
 cas no :123-31-9 rtecs no :MX3500000
 area : UN type : REC

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|subject|specification|descriptor|
|-----+-----+-----|
| TRNSP |                   | CLASS |
| LABEL  |                   | RQR   |
| PACK   |                   | RQR   |
|-----+-----+-----|
  
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UN No. 2662. Class: 6.1 = Toxic substance. Packing group: III = Low danger.

entry date: NOV 2000

title: UN Orange Book - Dangerous Goods List

original : !RTDGFK, Recommendations on the Transport of Dangerous Goods prepared by the United Nations Committee of Experts on the Transport of Dangerous Goods, 11th revised ed., , , 1999

