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COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS

Sub-Committee of Experts on the Transport of Dangerous Goods
(Twenty-third session, 30 June -4 July 2003, agenda item 6 (b))

LISTING, CLASSIFICATION AND PACKING

Classification of UN 2662 - Hydroquinone

Transmitted by the International Council of Chemical Associations (ICCA)

1. General

A review of available toxicological data from 1949 to 2002 indicates that the range of LD_{50} values for Oral Toxicity for HYDROQUINONE is between 298 mg/kg to 1,295 mg/kg of body weight for rats. The most current data reported for the LD_{50} value for Oral Toxicity for HYDROQUINONE is >375 mg/kg of body weight for rats from a 2002 study. These values are above the current UN Oral toxicity LD_{50} cut off point of 200 mg/kg of body weight for rats for packing group III Toxic Materials and the GHS cut off point of 300 mg/kg of body weight for rats for the Acute Toxicity Category 3 materials.

Overviews of the "Acute Toxicity of Hydroquinone in Rodents" and the "United Nations Data Sheet for New or Amended Classification of Substances" are included in this document.

2. Proposals

Proposal 1
ICCA proposes that the listing for **HYDROQUINONE**, UN 2662 be deleted from the Dangerous Goods List in Chapter 3.2 of the Model Regulations

Proposal 2
As a consequential amendment, delete HYDROQUINONE, 6.1, 2662 from the INDEX

Annex

THE ACUTE TOXICITY OF HYDROQUINONE IN RODENTS - AN OVERVIEW

Summary
The table below is a chronological description of the numerous acute oral toxicity studies conducted on hydroquinone (HYDROQUINONE) in rodents. Although there appears to be a wide variation in acute toxicity values, in general, all studies yielded values significantly greater than the 300 mg/kg cut off value established by the Subcommittee of Experts on the Globally Harmonized System for the Classification and Labelling of Chemicals for Acutely Toxic Materials. The variation in measured toxicity is likely attributable to the methodology employed in the studies, including whether the animals were fasted prior to exposure, the strain of rat used, and the possible presence of *p*-benzoquinone contaminant, which is significantly more toxic than HYDROQUINONE. Because the majority of the studies are quite dated, significant study methodology detail is missing that would assist in making sound conclusions regarding study robustness, overall quality, and reliability. The LD_{50} result of >375 mg/kg as determined by the Shepard (2002) study, is the only toxicity value derived using a standardized method with both sexes of rat in the fasted state, exposed to test material of documented purity. This study was conducted under Good Laboratory Practice (GLP) assurances and accordingly possesses the highest overall reliability.

Species	Result (mg/kg)	Reference
Rat	370 – 390	Hodge and Sterner, 1949
Rat	320	Woodard *et al.*, 1949
Rat	302	Woodard, 1951
Mice	390	Woodard, 1951
Rats	298 – 1,295	Carlson and Brewer, 1953
Rats	720	Mozhayev *et al.*, 1966
Mice	340	Mozhayev *et al.*, 1966
Rats	780	Anikeeva, 1974
Rats	680	Christian *et al.*, 1980
Rats	>375	Shepard, 2002 (Unpublished data)

Background and Review of Individual Studies

The acute oral toxicity of HYDROQUINONE in rodents has been evaluated in numerous studies, the vast majority of which were conducted prior to the establishment of standardized protocols and the enactment of GLP study assurances. These assurances promote study quality and the reliability of the results. While the results of the two studies in mice (390 and 340 mg/kg) were relatively similar to each other, a somewhat wider difference in values is observed with rats (298 – 1,295 mg/kg), with all but 2 studies significantly exceeding 300 mg/kg.

The wide range of values observed by Carlson and Brewer is attributed to both the strain of rat tested as well as to whether or not the test animals were fed or fasted prior to exposure, with the last factor being of most importance. These researchers assessed the toxicity of HYDROQUINONE in three rat strains, Priestly, Sprague-Dawley (SD), and Wistar. When exposures were conducted on non-fasted animals the LD_{50} ranged from 731 mg/kg in Wistars to 1,295 mg/kg in the Priestly strain. However, under fasting conditions prior to exposure the LD_{50} values decreased by 60 – 70%, with values in the SD strain ranging from 1,090 mg/kg to 323 mg/kg and from 731 mg/kg to 298 mg/kg in the Wistar strain. The reliability

and quality of this study is uncertain due to the time frame in which this study was conducted (early 1950's) and lack of study documentation (study was pre-GLP assurances enactment).

Similar concerns over study quality may be raised by the LD_{50} values of 302 and 320 reported by Woodard *et al*. (1949) and Woodard (1951). These studies are also quite old and were conducted as part of a Ph.D. dissertation. As such, they too lack GLP assurances and many methodology details associated with modern day studies. It was noted, however, that the rats were fasted prior to dosing. The strain of rat used (Osborne-Mandel "Yale" strain) may also have been a factor in the reported LD_{50} as evidenced by the work of Carlson and Brewer who demonstrated variation in LD_{50} based upon the specific strain exposed. Woodard used an interpolation method to derive the LD_{50} value, and this method is not as precise as those currently recommended. Another possible factor that could have contributed to the somewhat lower values obtained by Woodard is test material purity and the formation of *p*-Benzoquinone contaminant. *P*-Benzoquinone is significantly more toxic than HYDROQUINONE and, if present, could have led to a lower value than obtained in the 1949 study.

Study results reported by Mozhayev *et al.*, 1966 (720 mg/kg), Anikeeva, 1974 (780 mg/kg), and Christian *et al.*, 1980 (680 mg/kg) also possess lower reliabilities as all three of these studies are compromised by a lack of methodological detail and an absence of GLP study assurances. As already suggested by the results of Carlson and Brewer, the study variable of "fed or fasted" can play a significant role and may be the basis for their comparatively higher values. Nevertheless, these studies do report acute toxicity values that are significantly above the 300 mg/kg level of concern.

While the study by Hodge and Sterner is also dated, and accordingly possesses a low reliability, its results (370 – 390 mg/kg) are closer to those obtained by Carlson and Brewer in fasted SD rats (323 mg/kg) as well as the value of 320 mg/kg initially published by Woodard (1949) who also used fasted rats. Furthermore, the results of all these older studies corroborate the LD50 results of >375 mg/kg obtained by Shepard (2002) in SD rats. The study by Shepard is deemed to possess the highest overall reliability as it utilized standardized methods prescribed by the DOT, both sexes of rats, test material of known purity and is fully detailed, having been just recently conducted, and utilized GLP assurances.

Further support that the acute toxicity of HYDROQUINONE exceeds 300 mg/kg can be garnered from results of other short-term studies. Specifically, Carlson and Brewer reported a mortality rate of approximately 1.0% per day in SD rats exposed to 500 mg/kg by stomach tube 9 times in 12 days. While these rats were not fasted, they were able to tolerate multiple exposures to a high dose of HYDROQUINONE over a short period of time without a mortality rate exceeding 50%. Woodard (1951) also only reported 6 deaths in 20 rats exposed to 300 mg/kg in other experiments. In addition, no deaths were reported following a single dose of 350 mg/kg of radiolabeled HYDROQUINONE to Fischer 344 rats (unfasted) in a HYDROQUINONE metabolism study (Eastman Kodak Company 1988).

References

(1) Anikeeva, L.A. (1974). Effect of hydroquinone on the functional state on the liver. *Tr. Khark. Gos. Med. Inst.* **114**:65-66. Referenced in the Final Report of the Safety Assessment for Hydroquinone and Pyrocatechol. Prepared by the Expert Panel of the Cosmetic Ingredient Review. June 26, 1985.

(2) Carlson A.J. and Brewer, N.R. (1953). Toxicity studies on hydroquinone. *Proc. Soc. Exp. Bio. Med.* **84**:684-688.

(3) Christian, R.T., *et al.* (1980). The development of a test for the potability of water treated by a direct reuses system. U.S. Army Medical Research and Development Command. Washington, D.C. Contract No. DADA-17-73-C-3013. University of Cincinnati.

(4) Eastman Kodak Company (1988) (Unpublished data) Toxicokinetic studies with hydroquinone in male and female Fischer 344 rats. Health and Environmental Laboratories; Eastman Kodak Company; Rochester, NY.

(5) Hodge, H.C. and Sterner, J.H. (1949). Tabulation of toxicity classes. *Am Indus. Hyg. A. Quart.* **10**:93-96. Referenced in the Final Report of the Safety Assessment for Hydroquinone and Pyrocatechol. Prepared by the Expert Panel of the Cosmetic Ingredient Review. June 26, 1985.

(6) Mozhayev *et al.* (1966). The toxicity of hydroquinone in the case of chronic poisoning. *Farmakol. Toksikol.* (Moscow) **29**:238-240.

(7) Shepard, K.P. (2002)(Unpublished data). Acute oral toxicity study in the rat; Guidelines OECD: 401; EEC: Annex V., Test B.1; and U.S. DOT General Requirements for Shipments and Packagings 49CFR173.132. Health and Environmental Laboratories; Eastman Kodak Company; Rochester, NY.

(8) Woodard, G. *et al.* (1949). Toxicity of hydroquinone for laboratory animals. Fed. Proc. **8**:348.

(9) Woodard, G.D.L. (1951). The toxicity, mechanism of action, and metabolism of hydroquinone. Doctoral dissertation, George Washington University, Washington, D.C.

Figure 1

DATA SHEET TO BE SUBMITTED TO THE UNITED NATIONS FOR NEW OR AMENDED CLASSIFICATION OF SUBSTANCES

Submitted by the **International Council of Chemical Associations** Date **April 1, 2003**.....

Supply all relevant information including sources of basic classification data. Data should relate to the product in the form to be transported. State test methods. Answer all questions - if necessary state "not known" or "not applicable" - If data is not available in the form requested, provide what is available with details. Delete inappropriate words.

Section 1. SUBSTANCE IDENTITY

1.1 Chemical name **Hydroquinone** .....

1.2 Chemical formula **$C_6H_4(OH)_2$** .....

1.3 Other names/synonyms **1,4 Benzenediol, p-benzenediol, benzohydroquinone, benzoquinol, 1,4, dihydroxybenzene, p-dihydroxybenzenene, p-dioxobenzene, p-dioxybenzene, hydroquinol, hydroquinole, a-hydroquinone, p-hydroquinone, p-hydroxyphenol, quinol, B-quinol**.....

1.4.1 UN number **(existing: 2662) (proposed: None)** .....

1.4.2 CAS number **123-31-9**

1.5 Proposed classification for the Recommendations

1.5.1 Proper shipping name (3.1.2*) **None** .....

1.5.2 Class/division **None** ....subsidiary risk(s) **None** .....

Packing group **None** .....

1.5.3 Proposed special provisions, if any **None** .....

1.5.4 Proposed packing instruction(s) **None** .....

Section 2. PHYSICAL PROPERTIES

2.1 Melting point or range **170 °C**

2.2 Boiling point or range **286 °C**

2.3 Relative density at :

2.3.1 15 °C **1.332**.....

2.3.2 20 °C **Not known**.....

2.3.3 50 °C **Not known**.....

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* *This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.*

2.4 Vapour pressure at :

2.4.1 50 °C Not known at this temperature; **2.4x10-3 Pa at 25°C** ..... kPa

2.4.2 65 °C Not known ..... kPa

2.5 Viscosity at 20°C** **Not applicable**..... m^2/s

2.6 Solubility in water at 20°C..... **7** g/100 ml

2.7 Physical state at 20°C (2.2.1.1*) **SOLID** **

2.8 Appearance at normal transport temperatures, including colour and odour .....

White, long needle-like crystals that are odourless, less than 1% of particles are less than 100 microns in lengh

2.9 Other relevant physical properties **None**

Section 3. FLAMMABILITY

3.1 Flammable vapour

3.1.1 Flash point (2.3.3*) **165°C**.....**OC**

3.1.2 Is combustion sustained? (2.3.1.3*) **NO**

3.2 Autoignition temperature **515°C**

3.3 Flammability range (LEL/UEL) % - **Not applicable**

3.4 Is the substance a flammable solid? (2.4.2*) **NO**

3.4.1 If yes, give details .....
.....

Section 4. CHEMICAL PROPERTIES

4.1 Does the substance require inhibition/stabilization or other treatment such as nitrogen blanket to prevent hazardous reactivity ? **NO**
If yes, state

4.1.1 Inhibitor/stabilizer used .....

4.1.2 Alternative method.....

4.1.3 Time effective at 55°C.....

4.1.4 Conditions rendering it ineffective .....

4.2 Is the substance an explosive according to paragraph 2.1.1.1? (2.1*) **NO**

4.2.1 If yes, give details.....
.....

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* *This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.*

** *See definition of "liquid" in 1.2.1 of the Model Regulations on the Transport of Dangerous Goods.*

4.3 Is the substance a desensitized explosive? (2.4.2.4*) **NO**

4.3.1 If yes, give details

.....

4.4 Is the substance a self-reactive substance? (2.4.1*) **NO**

If yes, state

4.4.1 Exit box of flow chart.....

What is the self-accelerating decomposition temperature (SADT) for a 50 kg package? °C

Is the temperature control required? (2.4.2.3.4*) yes/no

4.4.2 Proposed control temperature for a 50 kg package ..... °C

4.4.3 Proposed emergency temperature for a 50 kg package..... °C

4.5 Is the substance pyrophoric? (2.4.3*) **NO**

4.5.1 If yes, give details.....
.....

4.6 Is the substance liable to self-heating? (2.4.3*) **NO**

4.6.1 If yes, give details.....
.....
.....

4.7 Is the substance an organic peroxide (2.5.1*) **NO**

If yes state

4.7.1 Exit box of flow chart.....

What is the self accelerating decomposition temperature (SADT) for a 50 kg package?..... °C

Is temperature control required? (2.5.3.4.1*) yes/no

4.7.2 Proposed control temperature for a 50 kg package ..... °C

4.7.3 Proposed emergency temperature for a 50 kg package..... °C

4.8 Does the substance in contact with water emit flammable gases? (2.4.4*) **NO**

4.8.1 If yes give details.....
.....
.....

4.9 Does the substance have oxidizing properties (2.5.1*) **NO**

4.9.1 If yes, give details.....
.....
.....

- *This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.*

4.10 Corrosivity (2.8*) to:

4.10.1 Mild steel **None** .....mm/year at ..... °C

4.10.2 Aluminium **None** .....mm/year at..... °C

4.10.3 Other packaging materials
(specify) **None**..... .....mm/year at.....
....mm/year at.....

4.11 Other relevant chemical properties. **Reacts with oxidizing agents. Dust explosions possible if the substance is transported as fine particles.** .....
.....

Section 5. HARMFUL BIOLOGICAL EFFECTS

5.1 LD 50, oral (2.6.2.1.1*) >**375** .....mg/kg Animal species **Rat (Both Sexes)**[9]

(OECD 401)

5.2 LD 50, dermal (2.6.2.1.2*) **>2000** .....mg/kg Animal species **Rabbit (Both Sexes)**[8]

(OECD 402, and 49CFR173.132)

5.3 LC 50, inhalation (2.6.2.1.3*) **Not applicable** mg/litre Exposure time ..... hours

(less than 1% of particles are less than 100 microns in length)

or ml/m^3 .....Animal species .....

5.4 Saturated vapour concentration at 20 ? C (2.6.2.2.4.3*) **Not applicable** ..... ml/m^3

Skin exposure (2.8*) results **Negative** Exposure time **24 hours** ..... hours/minutes
Animal species **Rabbit** .....

(OECD 402, and 49CFR173.132)

5.6 Other data **Hydroquinone exposure may cause eye irritation. Relatively high Hydroquinone exposure may contribute to conjunctivitis, corneal pigmentation, or structural irregularities.**[7]

5.7 Human experience **Most people are exposed to hydroquinone in the diet due to the presence of hydroquinone in everyday foods and beverages (e.g., wheat products, some teas, beer, red wine)[1,4,6]. The primary exposure route during manufacturing is through dermal contact or inhalation of dust particles[6]. However, the large particle size of the hydroquinone crystals (less than 1% of the particles are less than 100 microns long) is expected to limit dust inhalation. A study published in 1982 found found no association between workers exposed to hydroquinone during photographic processing and cancer[3]. In addition, a mortality study published in 1995 of workers exposed to hydroquinone found no association between hydroquinone exposure and cancer[7].**

* *This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.*

Section 6. SUPPLEMENTARY INFORMATION-

6.1 Recommended emergency action

6.1.1 Fire (include suitable and unsuitable extinguishing agents)

Use extinguishers containing dry chemical, alcohol-resistant foam, water, or carbon dioxide. Water used to control fires should be contained or diked, for subsequent disposa[2, 11, 12].....

6.1.2 Spillage

Rubber gloves and boots should be worn while cleaning up the spillage. The spilled substance should be swept into metal or fibreglass containers. A P2 respirator should be worn, if available. Remaining hydroquinone can be flushed away with water, but run-off should be prevented from entering the environment [2, 11, 12]. .....

6.2 Is it proposed to transport the substance in:

6.2.1 Intermediate Bulk Containers (6.5*)? **YES**

6.2.2 Portable tanks (6.7*) **NO**

If yes, give details in Sections 7 and/or 8.

Section 7. INTERMEDIATE BULK CONTAINERS (IBCs) (only complete if yes in 6.2.1*)

7.1 Proposed type(s) UN13H2**.....**

Section 8. MULTIMODAL TANK TRANSPORT (only complete if yes in 6.2.2)

8.1 Description of proposed tank (including IMO tank type if known) .....
.....

8.2 Minimum test pressure .....

8.3 Minimum shell thickness .....

8.4 Details of bottom openings, if any .....

8.5 Pressure relief arrangements.....

8.6 Degree of filling .....

8.7 Unsuitable construction materials .....

* *This and similar references are to chapters and paragraphs in the Model Regulations on the Transport of Dangerous Goods.*

8.8 References:

1. DeCaprio, A.P. "The Toxicology of Hydroquinone – Relevance to Occupational and Environmental Exposure." *Critical Reviews in Toxicology*, 29, 283-330. 1999.

2. Eastman Chemical Company, Kingsport, TN. Material Safety Data Sheet for Hydroquinone. Revised January 2001.

3. Friedlander, B.R., Hearne, F.T., Newman, B.J. Mortality, cancer incidence, and sickness-absence in photographic processors: an epidemiologic study. *J. Occup. Med*. 24, 605-613. 1982.

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5. Organization for Economic Cooperation and Development (OECD). Final SIAR (SIDS Initial Assessment Report): Hydroquinone. 1997.

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11. Mitsui Chemicals America Inc. Tokyo, Japan. Material Safety Data Sheet for Hydroquinone. Revised September 1999.

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