1,4-Benzenediol
(Hydroquinone)

Chemical Abstracts Service
Registry Number
123-31-9

Synopsis

The Ministers of the Environment and of Health have conducted a screening assessment of 1,4-benzenediol, Chemical Abstracts Service Registry Number (CAS RN) 123-31-9, a substance identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. It was identified as such because it was considered to pose greatest potential for exposure (GPE) to individuals in Canada and had been classified by other agencies on the basis of carcinogenicity and genotoxicity. While the substance did meet the ecological categorization criteria for inherent toxicity to aquatic organisms, it did not meet the criteria for persistence or bioaccumulation. Therefore, the focus of this assessment of 1,4-benzenediol relates to human health aspects.

Based on information reported pursuant to section 71 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the total quantity of 1,4-benzenediol imported into Canada in 2006 was between 100 000 kg and 1 000 000 kg. Uses of 1,4-benzenediol in Canada include the following: as a polymerization inhibitor in unsaturated polyester and methylmethacrylate resin monomers; as a stabilizer in colourants and various types of industrial and consumer adhesives, thread lockers and thread sealants; as an additive to heat shrink tubing, restorative paste, bonding tape, film tape and liquid bandages; as a performance additive in sheetfed printing and heatset inks; and as a reducing agent in photographic developer. 1,4-Benzenediol occurs naturally, including in various food items.

The predominant source of general population exposure to 1,4-benzenediol is expected to be as a result of its natural presence, or the presence of the glucose conjugate, 4-hydroxyphenyl-β-D-glucopyranoside (arbutin), in various food and beverages. Contributions to total exposure from the other media (ambient and indoor air, water and soil) are considered negligible in comparison.

There may also be dermal exposure to 1,4-benzenediol in consumer products such as photographic developers, adhesives, certain cosmetic products such as hair dyes, and various authorized skin lightening creams .

Based principally on the weight of evidence based assessment of the European Commission, the critical effect for the characterization of risk to human health is

carcinogenicity, based on the observation of tumours, including kidney tumours, in rats and mice chronically exposed to the substance (oral exposure). 1,4-Benzenediol was also genotoxic in several *in vitro* and *in vivo* assays. Therefore, although the mode of induction of tumours has not been fully elucidated, it cannot be precluded that the tumours observed in experimental animals resulted from direct interaction with genetic material.

On the basis of the carcinogenicity of 1,4-benzenediol, for which there may be a probability of harm at any level of exposure, it is concluded that 1,4-benzenediol is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of ecological hazard and reported releases of 1,4-benzenediol, it is concluded that this substance is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. Additionally, 1,4-benzenediol does not meet criteria for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

This substance will be included in the Domestic Substances List inventory update initiative, to be launched in 2009. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, 1,4-benzenediol meets one or more of the criteria set out in Section 64 of the *Canadian Environmental Protection Act, 1999*.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as the highest priorities.

The substance 1,4-benzenediol was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by another agency on the basis of carcinogenicity and genotoxicity. The Challenge for 1,4-benzenediol was published in the *Canada Gazette* on February 3, 2007 (Canada 2007a). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although 1,4-benzenediol was determined to be a high priority for assessment with respect to human health and it also met the ecological categorization criterion for inherent toxicity for aquatic organisms, it did not meet the criteria for potential for persistence or bioaccumulation. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

> "64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (*b*) constitute or may constitute a danger to the environment on which life depends; or
>
> (*c*) constitute or may constitute a danger in Canada to human life or health."

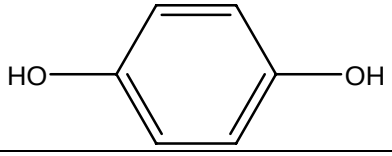
Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to September 2007. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including John Christopher (California Department of Toxic Substances Control), Michael Jayjock (The Lifeline Group), Donna Vorhees (The Science Collaborative) and Joan Strawson (TERA). Comments on these sections were also received from Exponent. While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

Table 1:. Substance identity

CAS Registry Number	123-31-9
DSL name	1,4-Benzenediol
Inventory names[1]	1,4-Benzenediol (TSCA, DSL, ENCS, AICS, ECL, SWISS, PICCS, ASIA-PAC, NZIoC) Hydroquinone (DSL, EINECS, PICCS) Hydrochinon (EINECS, SWISS, PICCS) Benzene, 1,4-dihydroxy- (PICCS) P-dihydroxybenzene (PICCS) P-hydroxyphenol (PICCS)
Other names	Hydroquinone; 1,4-Benzoquinol; 1,4-Dihydroxybenzene; 4-Hydroxyphenol; Aida; Arctuvin; Benzohydroquinone; Benzoquinol; Black & White Bleaching Cream; BQ(H); Diak 5; Dihydroquinone; Eldopacque; Eldopaque; Eldopaque Forte; Eldoquin; Eldoquin Forte; HE 5; Hydroquinol; NSC 9247; p-Benzenediol; p-Dihydroquinone; p-Dioxybenzene; p-Hydroquinone; p-Phenylenediol; p-Quinol; Phiaquin; Quinol; Solaquin Forte; Tecquinol; Tenox HQ; UN 2662; UN 2662 (DOT)
Chemical group	Discrete organics
Chemical sub-group	Phenols
Chemical formula	$C_6H_6O_2$
Chemical structure	
SMILES	Oc(ccc(O)c1)c1
Molecular mass	110.11 g/mol

1 **Source**: National Chemical Inventories (NCI), 2007: AICS (Australian Inventory of Chemical Substances); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Chemical Substances); ELINCS (European List of Notified Chemical Substances), ENCS (Japanese Existing and New Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances); TSCA (Toxic Substances Control Act Chemical Substance Inventory); ASIA-PAC (Combined Inventories from the Asia-Pacific Region); and NZIoC (New Zealand Inventory of Chemicals)

Physical and Chemical Properties

Table 2. Physical and chemical properties of hydroquinone

Property	Type	Value	Temperature (°C)	Reference
Melting point (°C)	Experimental	169		OECD SIDS 2002
Boiling point (°C)	Experimental	286		OECD SIDS 2002
Density (kg/m^3)	Experimental	1.341		OECD SIDS 2002
Vapour pressure (Pa)	Experimental	2.34×10^{-3}	25	OECD SIDS 2002
Henry's Law constant ($atm\text{-}m^{-3}$ / mol)	Experimental	3.84×10^{-11}		OECD SIDS 2002 (Meylan and Howard 1991)
Dissociation constant	Experimental	pK1= 9.9		OECD SIDS 2002
Log K_{ow}	Experimental	0.59		Hansch et al. 1995
Log K_{oc}	Modelled	2.64		PCKOCWIN v1.66
Water solubility (mg/L)	Experimental	73 000		OECD SIDS 2002 (Sterner et al. 1947)

Sources

1,4-Benzenediol occurs naturally as a conjugate with beta-D-glucopyranoside in the leaves, bark and fruit of a number of plants, especially the ericaceous shrubs such as cranberry, cowberry, bearberry and blueberry (Varagnat 1982; Harbison and Belly 1982; Hudnall 1987). It has been detected at low levels in coffee, tea, red wine, beer, cola soft drinks, 2% milk, orange juice, corn, wheat and rice cereals, wheat germ and various fruits, including pears, oranges, cantaloupes, cherries, asparagus, apples, blueberries and cranberries (Deisinger et al. 1996). 1,4-Benzenediol is known to play a role in the defence mechanisms of certain classes of beetles (Aneshansley et al. 1969). It is also known to be present in the particulate fraction of cigarette smoke (IARC 1985).

1,4-Benzenediol is manufactured by the oxidation of aniline to quinone and the subsequent reduction of quinone to 1,4-benzenediol (Kirk-Othmer 1966). Other routes of synthesis include the oxidative cleavage of diisopropyl benzene and the hydroxylation of phenol (OECD SIDS 2002). According to current information reported pursuant to the

CEPA 1999 section 71 notice with respect to 1,4-benzenediol, 17 Canadian companies and 2 foreign companies reported importing 1,4-benzenediol (whether alone, in a product, in a mixture or in a manufactured item) in 2006 in a quantity greater than or equal to 100 kg while another 10 Canadian companies reported importing 1,4-benzenediol (whether alone, in a product, in a mixture or in a manufactured item) in 2006 in a quantity less than 100 kg. No Canadian companies manufactured 1,4-benzenediol in a quantity above 100 kg in Canada in 2006 (Environment Canada 2007; Chemical Economics Handbook 2006). The total quantity imported was between 100,000 kg and 1,000,000 kg (Environment Canada 2007).

Uses

According to the submissions made under section 71 of CEPA 1999, the known current uses of 1,4-benzenediol in Canada include the following: as a polymerization inhibitor in unsaturated polyester and methylmethacrylate resin monomers; as a stabilizer in colourants and various types of industrial and consumer adhesives, thread lockers and thread sealants; as an additive to heat shrink tubing, restorative paste, bonding tape, film tape, liquid bandages, etc; as a performance additive in sheetfed printing and heatset inks; and as a reducing agent in photographic developers (Environment Canada 2007).

A number of other uses of 1,4-benzenediol in Canada have also been identified. Although prohibited for use in cosmetic products applied to the skin and mucous membranes, including skin whitening products (Health Canada 2007a), there were 110 notifications of cosmetic products containing 1,4-benzenediol filed with Health Canada under the Cosmetic Regulations of the *Food and Drugs Act*, primarily in manicure preparations and hair dyes, at concentrations ranging up to 3% (Health Canada, 2007b). Health Canada's Drug Product Database lists over 90 DIN-assigned drugs containing 1,4-benzenediol at concentrations ranging from < 2% to 4%. Provincially, the National Association of Pharmacy Regulatory Authorities (NAPRA) lists 1,4-benzenediol topical preparations as Schedule II drugs which are less strictly regulated and do not require a prescription but do require professional intervention from the pharmacist at the point of sale and possibly referral to a practitioner. They are available only from the pharmacist and must be kept within an area of the pharmacy where there is no public access and no opportunity for patient self-selection (www.napra.ca) (Health Canada 2007c). 1,4-Benzenediol is also present at 0.3% concentration as a stabilizer in two pest control products registered under the *Pest Control Products Act*. One product is a restricted-class herbicide for use in irrigation canals to control vegetation and the second product is a commercial-class microbiocide used in oilfield recovery systems (PMRA 2007).

1,4-Benzenediol may also be used as a chemical intermediate in the synthesis of the following types of chemicals: antioxidants and antiozonants used in rubber processing; antioxidants used in industrial fats, oils and foods; and stabilizers for paints, varnishes, motor oils and fuels. It is used in the photographic industry for the development of black-and-white film and hospital X-rays and also in lithography. It has also been reported as a

component of casting compounds, and may be used as a corrosion inhibitor in boilers and cooling towers (OECD SIDS 2002).

Releases to the Environment

Anthropogenic releases of 1,4-benzenediol may occur during its production and use in photographic applications, antioxidants, monomer inhibitors, dyes and pigments, agricultural chemicals and as a stabilizer in paints and varnishes, motor fuels and oils. It may also be released to the environment in the effluent of photographic processes (HSDB 2006). Table 3 summarizes on-site releases and off-site disposal of 1,4-benzenediol (and its salts) to unspecified media from industrial facilities in Canada from 2001 to 2006, as reported in the National Pollutant Release Inventory (NPRI 2007).

Table 3. Releases of 1,4-benzenediol for 2001–2006

Year	On-site releases	Off-site disposal	Release units
2006	2	0	kg
2005	2	1	kg
2004	2	49	kg
2003	2	1	kg
2002	0	1	kg
2001	1	1	kg

According to the submissions made under section 71 of CEPA 1999, 3 Canadian companies have reported releases of 1,4-benzenediol (whether alone, in a product, in a mixture or in a manufactured item) totalling 103 kg in the 2006 calendar year (Environment Canada 2007).

Environmental Fate

As indicated in Table 2, 1,4-benzenediol has a very high solubility in water and a moderate soil adsorption coefficient, which suggests that if released to water, adsorption of 1,4-benzenediol to sediment and suspended organic matter would not be important. If released to soil, 1,4-benzenediol is expected to largely remain in soil, with minor partitioning into water. If released to the atmosphere, 1,4-benzenediol is expected to undergo direct photochemical degradation (Tables 5a,b). 1,4-Benzenediol may also be removed from the atmosphere by wet deposition processes, considering the very high water solubility of this chemical (HSDB 2006).

The results of a Level III fugacity model, which predicts the distribution of 1,4-benzenediol in the environment following release to various media, are summarized in Table 4.

Table 4. Results of the Level III fugacity modelling (EPIWIN V3.12) for 1,4-benzenediol

	Fraction of substance partitioning into each compartment medium (%)			
Substance released to	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	0.00	24.1	75.9	0.05
Water (100%)	0.00	99.8	0.00	0.19
Soil (100%)	0.00	20.2	79.8	0.04
Air, water, soil (33.3% each)	0.00	37.1	62.9	0.07

Persistence and Bioaccumulation Potential

Persistence

Based on the physical and chemical properties (Table 2) and the empirical and modelled data presented below (Tables 5a,b), 1,4-benzenediol does not meet the persistence criteria (half-lives in soil and water ≥ 182 days, in sediments ≥ 365 days, in air ≥ 2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 5a. Empirical data for persistence of 1,4-benzenediol

Medium	Fate process	Degradation value	Degradation endpoint/units	Test duration	Reference
Air	Photolysis	57	Photo-mineralization, %	17 hours	Freitag et al. 1985
Water	Biodegradation	70	Biodegradation, %	28 days	Chemicals Inspection and Testing Institute 1992

Table 5b. Modelled data for persistence of 1,4-benzenediol

Medium	Fate process	Degradation value	Endpoint/units	Reference
Air	Atm. oxidation	0.4606	Half-life, days	AOPWIN v1.91
Air	Ozone reaction	Non-reactive	Half-life, days	AOPWIN v1.91
Water	Biodegradation	15	Half-life, days	BIOWIN v4.02, Ultimate survey
Water	Biodegradation	0.691	Probability	BIOWIN v4.02, MITI Non-linear Probability
Water	Biodegradation	0.546	Probability	BIOWIN v4.02, MITI Linear Probability
Water	Biodegradation	0.918	Probability	Topkat v.6.1

Bioaccumulation

The experimental and modelled data (Tables 6a,b) indicate that the substance 1,4-benzenediol does not meet the bioaccumulation criteria (bioconcentration factor (BCF) / bioaccumulation factor (BAF) ≥ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 6a. Experimental data for bioaccumulation of 1,4-benzenediol

Test organism	Endpoint	Value wet wt L/kg	Reference (ECOTOX database)
Green algae (*Chlorella fusca*)	BCF	35–65	306; 11297; 17318
Fish (*Leuciscus idus; Leuciscus idus melanotus*)	BCF	40	3781; 17318

Table 6b. Predicted bioaccumulation values for 1,4-benzenediol

Test organism	Endpoint	Value wet wt L/kg	Reference
Fish	BAF	1	Modified Gobas BAF T2MTL (Arnot and Gobas 2003)
Fish	BCF	1–19	OASIS; Modified Gobas BCF 5% T2LTL (Arnot and Gobas 2003); BCFWIN v2.15

Potential to Cause Ecological Harm

As indicated earlier, 1,4-benzenediol does not meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Experimental ecotoxicological data for 4-benzenediol (ECOTOX database) indicate high toxicity to aquatic organisms. Acute LC_{50}/EC_{50} values are below 1 mg/L for fish and water flea, and as low as 0.044 mg/L for fish. Green algae and brine shrimp appear to be less sensitive (Acute LC_{50}/EC_{50}: 17-31 mg/L). No toxicity data for non-aquatic non-mammalian organisms were identified.

The National Pollutant Release Inventory reports releases of up to 2 kg per year to unspecified media for the years 2001-2006 (NPRI 2007). According to the submissions made under Section 71 of CEPA 1999, three Canadian companies had a combined hydroquinone release of just over 100 kg in 2006 (Environment Canada, 2007). Given the quantity and nature of these releases, they are not expected to result in significant exposure of organisms in the environment.

Based on the information available, 1,4-benzenediol is unlikely to be causing ecological harm in Canada.

Potential to Cause Harm to Human Health

Exposure Assessment

Appendix 1 presents upper-bounding estimates of 1,4-benzenediol intake for each age group in the general population of Canada, based upon maximum identified concentrations in environmental media and food items. The upper-bounding estimate of exposure to 1,4-benzenediol for the general population ranges from 91.32 µg/kg-bw (kilogram of body weight) per day for the 60+ age group to 393.45 µg/kg-bw per day in the 0–6 month (not formula fed) age group. Based on these estimates, intake from food and beverages represents the predominant source of exposure to 1,4-benzenediol for the general population of Canada, comprising over 99% of total exposure for all age groups. As indicated earlier,1,4-benzenediol and its glucose conjugate, 4-hydroxyphenyl-β-D-glucopyranoside (arbutin), are naturally present in many foods and beverages. Since arbutin is reported to hydrolyze readily in dilute acidic solutions to yield D-glucose and 1,4-benzenediol, ingested arbutin is expected to be converted to free 1,4-benzenediol in the stomach (Deisinger et al. 1996). As such, both measured concentrations of 1,4-benzenediol and arbutin in food and beverages were considered in deriving estimates of intake from food and beverages. Contributions to total intake from other media (ambient and indoor air, water and soil) were considered to be negligible in comparison to intake from food and beverages.

Dermal exposure during the use of consumer products containing 1,4-benzenediol can also contribute to total exposure for the general population. Appendix 2 presents a number of upper-bounding exposure scenarios for different products containing 1,4-benzenediol. These include intake from the use of black-and-white photographic developer (7.9×10^{-4} µg/kg-bw/day), household adhesives (7.2×10^{-5} µg/kg-bw/day), manicure preparations (3.0×10^{-4} µg/kg-bw/day) and oxidative hair dyes (7.5×10^{-3} µg/kg-bw/day). Because of the low vapour pressure of 1,4-benzenediol, it is considered unlikely that there will be any significant inhalation exposure associated with any of these uses. With regards to exposure resulting from the use of photodevelopers, the results from a recent study involving the biological monitoring of professional darkroom workers in the United Kingdom indicated no increase in the urinary excretion of 1,4-benzenediol for exposed workers, indicating that even for this potentially highly exposed population, intake of 1,4-benzenediol from use of developing solutions is unlikely to be a concern (UKHSE 1993).

Exposure estimates were not derived for skin lightening preparations containing 1,4-benzenediol, regulated under the *Food and Drugs Act*, due to the wide range of potential clinical uses. Additionally, access to these products is controlled through provisions established by the National Association of Pharmacy Regulatory Authorities.

1,4-Benzenediol is known to be present in the particulate fraction of cigarette smoke (IARC 1985) and this may also contribute to overall exposure.

Confidence in the upper-bounding estimate of intake of 1,4-benzenediol in environmental media is considered to be moderate, as limited measured concentrations were available. Confidence in the estimates of exposure estimates from use of consumer products containing 1,4-benzenediol is considered to be low, as they are based on assumptions; the estimates of exposure resulting from these uses, however, are considered to be overestimates of actual exposure.

Health Effects Assessment

Appendix 3 contains a summary of the available health effects information of 1,4-benzenediol in experimental animals. An overview of health effects reported in humans is presented in Appendix 4.

The European Commission (EC) has classified 1,4-benzenediol as a Category 3 carcinogen - "causes concern for humans owing to possible carcinogenic effects" (EC 1997a; IUCLID 2000). 1,4-Benzenediol was originally proposed as a category 2 carcinogen based on the evidence of development of kidney adenomas and mononuclear cell leukemia in rats and liver adenomas in mice (Appendix 3). However, the majority of EC experts agreed to classification as a category 3 carcinogen as only benign tumors were produced following exposure to this substance in experimental animals (EC 1997a; 1997b). The International Agency for Research on Cancer (IARC) has classified 1,4-benzenediol in Group 3 ("not classifiable as to its carcinogenicity to humans"), based upon inadequate evidence for carcinogenicity in humans and limited evidence in experimental animals (IARC 1999).

Long-term (2-year) exposure to 1,4-benzenediol via gavage (5 days/week) in male and female F344 rats at doses of 0, 25 or 50 mg/kg caused a dose-dependent increase in the incidence of renal tubular cell adenoma in male rats. In female rats, the incidence of mononuclear cell leukemia increased in a dose-dependent manner, but females developed less severe nephropathy than males. With a similar dosing regime, male and female B6C3F1 mice exposed to 0, 50 or 100 mg/kg 1,4-benzenediol showed an increase in relative liver weights in dosed males and high-dose females. In male mice, the compound-related lesions in the liver included fatty change, cytomegaly and syncytial cell alterations and the combined incidence of hepatocellular adenoma and carcinoma was found statistically non-significant. However, there was a significant increase in the incidence of hepatocellular adenomas in dosed female mice as compared to control (NTP 1989).

Administration of 0.8% 1,4-benzenediol in the diet for 104 or 96 weeks in rats and mice, respectively, induced hyperplasia of renal tubular cells and epithelia of renal papilla, as well as adenomas, predominantly in males of both species, and was associated with chronic nephropathy in male rats. Female rats showed slight nephropathy. The average daily intake was reported as 351 or 368 mg/kg-bw/day for male or female rats, respectively and 1046 and 1486 mg/kg-bw/day for male and female mice, respectively. The incidence of epithelial hyperplasia of renal papilla, renal tubular hyperplasia and tubular adenomas was significantly higher in male rats, while female rats showed slight

nephropathy. In mice, there was a significant increase in the incidence of hyperplasia of forestomach epithelium (squamous cells) in males and females; however, renal tubular hyperplasia and adenomas increased only in males. Also, the incidence of hepatocellular adenoma was enhanced in male mice (Shibata et al. 1991).

The European Commission (EC) has classified 1,4-benzenediol as a Category 3 mutagen ("a substance which causes concern for man owing to possible mutagenic effects") (EC 1997a; OJEC 2001). The EC specialized experts agreed that 1,4-benzenediol was a clear *in vitro* mutagen as well as *in vivo* somatic mutagen (EC 1997a). Genotoxicity studies showed positive results in many *in vivo* and *in vitro* test systems. The IARC (1999) concluded that 1,4-benzenediol was mutagenic in many *in vitro* systems and that it induced structural chromosome aberrations in mouse bone-marrow cells following intraperitoneal (ip) injection.

Although a mode-of-action analysis is beyond the scope of this screening assessment, nongenotoxic mechanisms have been proposed for the carcinogenicity of 1,4-benzenediol. It has been proposed that renal tubular cell adenomas may have developed in rats by an indirect mechanism which could have exacerbated a common disease of aging rats (i.e., chronic progressive nephropathy or CPN) following exposure to 1,4-benzenediol or its metabolite (McGregor 2007). However, a potential role of genetic damage in carcinogenicity of 1,4-benzenediol cannot be precluded. It is possible that 1,4-benzenediol may act through an indirect mechanism of genotoxicity (e.g. aneuploidy, oxidative stress, inhibition of DNA synthesis or cytotoxicity) for which, a threshold level may exist (Pratt and Barron 2003). There is some evidence that macromolecular binding and oxidative damage potential of 1,4-benzendiol is associated with its genotoxicity (Tsutsui et al. 1997; do Ceu Silva et al. 2003, 2004). The reaction of 1,4-benzendiol metabolites with glutathione and epigenetic damage caused by 1,4-benzendiol have also been suggested to cause kidney damage or leukemia (English et al. 1994; Whysner et al. 1995; McDonald et al. 2001). Additionally, 1,4-benzenediol is a metabolite of benzene, which has been classified as a Group 1 human carcinogen (IARC 1987).

With respect to non-cancer effects, the lowest oral no-observed-effects level (NOEL) in the database is 15 mg/kg-bw/day. In a two-generation reproduction study, male and female rats were administered (by gavage) 0, 15, 50 or 150 mg/kg-bw/day 1,4-benzenediol. No significant reproductive effects were seen in the F0 or F1 generation at the two low doses. Tremors were reported in 1/30 animals in the 50 mg/kg-bw/day group. The parental NOEL (general toxicity) was identified as 15 mg/kg-bw/day and a NOEL for parental and F1 generation reproductive toxicity was identified as 150 mg/kg/day (Blacker et al. 1993). In a 90-day dermal study in rats, a no-observed-adverse-effects level (NOAEL) of 73.9 mg/kg-bw/day was identified in male rats based on local effects; no systemic effects were reported (David 1994).

Confidence in the toxicological database is considered low to moderate. The health effects database does not comprehensively address key routes and durations of exposure.

Characterization of Risk to Human Health

Based principally on the assessment of the European Commission, a critical effect for characterization of risk to human health is carcinogenicity, for which a mode of induction involving direct interaction with genetic material cannot be precluded.

With respect to non-cancer effects, the lowest oral NOEL (15 mg/kg-bw/day) is from the rat 2-generation reproduction study, based on parental toxicity. However, given that the predominant source of exposure to the general population is through the naturally occurring presence of 1,4-benzenediol in foods and beverages, derivation of a margin of exposure between effect levels in dietary studies with experimental animals and upper-bounding estimates of exposure would not be meaningful. For non-cancer effects, the incremental exposure and risk associated with 1,4-benzenediol in environmental media resulting from its manufacturing and industrial uses is considered to be negligible.

Dermal exposure to 1,4-benzenediol from use of consumer products can occur (see Appendix 2). The consumer product scenario with the highest potential dermal exposure is contact with oxidative hair dye containing 1,4-benzenediol (7.5×10^{-3} µg/kg-bw/day). There is a margin of exposure of well over 1,000,000 between this value and the dermal NOAEL of 73.9 mg/kg-bw/day in the 90-day rat study. With respect to non-cancer effects via the dermal route, this margin is considered adequate to account for uncertainty in the database on exposure and effects.

Risks associated with skin-lightening preparations containing 1,4-benzenediol, regulated under the *Food and Drugs Act*, need to be considered together with the clinical benefits of the preparations, which is beyond the scope of this screening assessment. However, Health Canada has received 10 reports (between January 01, 1965 to November 30, 2007) of adverse reactions suspected to be associated with the use of over-the-counter skin lightening creams (Health Canada, 2007d).

Uncertainties in Evaluation of Risk to Human Health

There is uncertainty regarding interspecies differences in sensitivity to 1,4-benzenediol. The scope of this screening assessment does not take into consideration a mode-of-action analysis for carcinogenicity.

Data on concentrations of 1,4-benzenediol in environmental media were limited. There is also uncertainty with respect to estimates of exposure from use of consumer products, as they are based on conservative assumptions.

Conclusion

On the basis of the carcinogenicity of 1,4-benzenediol, for which there may be a probability of harm at any level of exposure, it is concluded that 1,4-benzenediol is a

substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Based on the available information, it is concluded that 1,4-benzenediol is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

It is therefore concluded that 1,4-benzenediol does not meet the criteria in paragraph 64a and 64b of CEPA 1999, but it does meet the criteria in paragraph 64c of CEPA 1999. Additionally, 1,4-benzenediol does not meet criteria for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations.*

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Appendix 1. Upper-bounding estimates of daily intake of 1,4-benzenediol for the general population in Canada

Route of exposure	Estimated intake (µg/kg-bw per day) of 1,4-benzenediol by various age groups						
	0–6 months[1, 2, 3]		0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	formula fed	not formula fed					
Air[9]	0.01		0.03	0.05	0.05	0.06	0.05
Drinking water[10]	0.00	0.20	0.10	0.10	0.05	0.04	0.04
Food and beverages[11]		393.24	366.35	242.46	127.65	105.19	91.27
Soil[12]	0.00		0.00	0.00	0.00	0.00	0.00
Total intake	0.00	393.45	366.45	242.56	127.71	105.23	91.32

1 No data were reported for concentration of 1,4-benzenediol in breast milk.

2 Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (EHD 1998).

3 For formula-fed infants, intake from water is synonymous with intake from food. No data on concentrations of 1,4-benzenediol in formulae were identified for Canada.

4 Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (EHD 1998).

5 Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (EHD 1998).

6 Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (EHD 1998).

7 Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (EHD 1998).

8 Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (EHD 1998).

9 No Canadian data were identified. As a surrogate, an atmospheric concentration of 0.00346 µg/m^3 of 1,4-benzenediol in fine particulate matter collected during an ambient air monitoring study conducted in Fresno, California was used to calculate the upper-bounding limit of exposure estimate (Schauer and Cass 2000). Since no indoor air concentration data were identified, it is assumed that the indoor air concentration would be equal to the ambient air concentration reported above, and that Canadians would be exposed to this concentration for 24 hours/day.

10 No Canadian data were identified. As a surrogate, the mean concentration of 7.6 µg/L, from a sample of water from the Mert River in Turkey, was used to calculate the upper-bounding limit of exposure estimate (Asan and Isildak 2003). For formula-fed infants, the concentration of 1,4-benzenediol in surface water used to reconstitute formula accounts for the intake of 1,4-benzenediol from food.

11 Reported maximum concentrations of 1,4-benzenediol in food from other countries were used as surrogate data when no Canadian data available. Estimates of intake from food are based upon concentrations in foods that are selected to represent the 12 food groups addressed in calculating intake (EHD 1998):

Dairy products: 30 µg/kg; mean concentration (total 1,4-benzenediol) in yogurt (Deisinger et al. 1996)

Fats: no data identified

Fruits: 15 090 µg/kg; mean concentration (total 1,4-benzenediol) in pear d'Anjou (Deisinger et al. 1996)

Vegetables: 480 µg/kg; mean concentration (total 1,4-benzenediol) in onions (Deisinger et al. 1996)
Cereal products: 10 650 µg/kg; mean concentration (total 1,4-benzenediol) in wheat germ (Deisinger et al. 1996);
Meat and poultry: no data identified
Fish: no data identified
Eggs: no data identified
Foods primarily sugar: no data identified
Mixed dishes and soups: no data identified
Nuts and seeds: no data identified
Soft drinks, alcohol, coffee, tea: 430 µg/kg; mean concentration (total 1,4-benzenediol) in red wine (Deisinger et al. 1996)

Amounts of foods consumed on a daily basis by each age group are described by Health Canada (EHD 1998). It should be noted that all concentrations of 1,4-benzenediol reported in foods are naturally occurring.

[12] No reported data for the concentration of 1,4-benzenediol in soil was identified. For the purposes of intake calculations, it was assumed that the concentration of 1,4-benzenediol in soil was 0.0 ng/g.

Appendix 2. Estimates of dermal exposure to 1,4-benzenediol from consumer products by adult Canadians

Consumer product type	Assumptions	Estimated exposure (µg/kg-bw/day)
Photograph developing solution for printing black-and-white photographs [1]	- Assuming a permeability coefficient of 9.3 x 10^{-6} cm/hr (Barber et al 1995); - assuming an exposed surface area of 20 cm^2. This is an estimated value based on consideration of an exposed surface area of 200 cm^2 (Versar 1986) and public comment received that indicates only the fingertips of one hand will likely be exposed during the development process. -assuming a frequency of use of 12 events/yr, a solution density of ~1.0 g/cm^3 and a wt. fraction of 1,4-benzenediol in developer solution of 0.037 (Versar Inc. 1986) While the weight fractions of 1,4-benzenediol in various commercial and consumer photodeveloper products reported in the section 71survey ranged from ~0.022–0.14 (Environment Canada 2007), the value reported in Versar was considered to be representative of the working concentration typically found in a home hobbyist photodeveloper solution. - assuming a total exposure time of 15 minutes. This was an estimated value based on consideration of an average darkroom session of 8 hrs (Versar 1986) and public comment received indicating that actual contact time with the developer solution during the development process will be brief as the photo hobbyist would be expected to wipe his/her hands after immersion in the developer solution to reduce contamination of post-developer solutions with developer. This value would be an overestimate if the hobbyist was to follow recommended safe handling procedures for this product by wearing protective gloves and/or using tongs rather than fingertips to insert and remove the photographs from the developer solution. - assuming a body weight of 70.9 kg (EHD 1998) Dose = (permeability coefficient) x (weight fraction) x (product density) x (exposure time) x (surface area exposed) x (frequency of use) x conversion factor / (body weight) Dose = (9.3 x 10^{-6} cm/hr) x (0.037) x (1.0 g/cm^3) x (0.25 hr) x (20 cm^2) x (12 events/yr /365 days/yr) x (1 x 10^6 µg/g) / (70.9 kg-bw)	7.9 x 10^{-4}
Component of household adhesive [1, 2]	- Assuming a permeability coefficient of 9.3 x 10^{-6} cm/hr (Barber et al 1995); - assuming a frequency of use of 12 events/yr, an exposed surface area of 2 cm^2 and an exposure time (application duration) of 0.083 hr (RIVM 2006); - assuming wt. fraction of 1,4-benzenediol in adhesive is 0.01 (Environment Canada 2007) - assuming a product density of ~1.0 g/cm^3 (Versar 1986) - assuming a body weight of 70.9 kg (EHD 1998) Dose = (permeability coefficient) x (weight fraction) x (density of product) x (exposure time) x (surface area exposed) x (frequency of use) x conversion factor / (body weight) Dose = (9.3 x 10^{-6} cm/hr) x (0.01) x (1.0 g/cm^3) x (0.083 hr) x (2 cm^2) x (12 events/yr /365 days/yr) x (1 x 10^6 µg/g) / (70.9 kg-bw)	7.2 x 10^{-5}
Manicure preparation[3, 4]	- Assuming dermal absorption rate of 0.52 ± 0.13 µg/cm^2/hr (Barber et al 1995);	

Consumer product type	**Assumptions**	**Estimated exposure** (µg/kg-bw/day)
	- assuming a frequency of use of 0.035 events/day, an exposure duration of 0.25 hr and a body weight of 60 kg (Health Canada 2007b) - assuming a mean exposed surface area of 4 cm^2 (RIVM 2006) Dose = (dermal absorption rate) x (surface area exposed) x (frequency of use) x (exposure duration) / (body weight) Dose = (0.52 µg/cm^2/hr) x (4 cm^2) x (0.035 events/day) x (0.25 hr) / (60 kg-bw)	3.0×10^{-4}
Oxidative hair dye [3]	- Assuming dermal absorption rate of 0.52 ± 0.13 µg/cm^2/hr (Barber et al 1995); - assuming a frequency of use of 0.03 events/day, a body weight of 60 kg, a mean exposed surface area of 580 cm^2, an exposure duration of 0.5 hr and a retention factor of 0.1 (Health Canada 2007b) Dose = (dermal absorption rate) x (surface area exposed) x (frequency of use) x (retention factor) x (exposure duration) / (body weight) Dose = (0.52 µg/cm^2/hr) x (580 cm^2) x (0.03 events/day) x (0.1) x 0.5 hr / (60 kg-bw) The hair dyes are of the oxidative type and the concentration of the 1,4-benzenediol component, typically 0.1 to 0.3%, will be reduced when the hair dye is mixed with hydrogen peroxide prior to application.	7.5×10^{-3}

[1] Since these products are used primarily by adults (20–59 years old), estimated exposures have been derived for this age group only. Body weight of 70.9 kg for an average Canadian adult was used (EHD 1998).

[2] Cyanoacrylate type (i.e., Super Glue) adhesive

[3] Body weight of 60 kg for an average Canadian adult female was used (Health Canada 2007b)

[4] In the case of artificial nail preparations, exposure to 1,4-benzenediol will occur mainly during application of the liquid resin to the nail plate. Since 1,4-benzenediol will be rapidly consumed during the polymerization process and any remaining residue will be trapped within the hardened polyacrylate matrix, any additional exposure following the initial application will likely be negligible.

Appendix 3. Summary of health effects information for 1,4-benzenediol

Endpoint	Lowest effect levels[1] / Results
Acute toxicity	**Lowest oral LD_{50}** = 298 mg/kg-bw (Wistar rats – fasted) Range = 298–1295 mg/kg-bw between different rat strains (Carlson and Brewer 1953) [cited in OECD 2002]. [Additional studies: Woodard 1951] **Lowest oral LD_{50}** = 390 mg/kg-bw (unfasted Swiss-mice) (Woodard 1951) [cited in OECD 2002]. [Additional studies: Carlson and Brewer 1953]. **Lowest dermal LD_{50}** = > 1000 mg/kg-bw (Guinea pig) (Toxicity Report 1971) [cited in OECD 2002].
Short-term repeated-dose toxicity	<u>14-day exposure:</u> **Lowest oral NOEL** = 250 mg/kg-bw/day (F344 rats) (NTP 1989). Male and female rats were administered repeat doses (0, 63, 125, 250, 500 or 1000 mg/kg-bw/day) 1,4-benzenediol via gavage for 14 days. The authors reported decreased body weight, tremors, and death in 500 and 1000 mg/kg groups. **Lowest oral NOEL** = 125 mg/kg-bw/day (male B6C3F1 mice) (NTP 1989). **Lowest oral NOEL** = 250 mg/kg-bw/day (female B6C3F1mice). Male and female mice were administered repeat doses (0, 31, 63, 125, 250 or 500 mg/kg-bw/day) 1,4-benzenediol via gavage for 14 days. Tremors followed by recovery or convulsion and death were reported at 250 mg/kg-bw/day and above in males and at 500 m/kg-bw/day in females. **Lowest dermal NOEL** = 1920 mg/kg-bw/day (male and female F344 rats) (NTP 1989) [cited in OECD 2002]. Male and female rats were topically (clipped back skin) administered 12 doses (0, 240, 480, 960, 1920 or 3840 mg/kg-bw/day) 1,4-benzenediol for 14 days. The authors reported no clinical signs of toxicity in any treatment group. Mean body weights were 6% lower in the 3840 mg/kg-bw/day group as compared to control. **Lowest dermal NOEL** = 4800 mg/kg-bw/day (male and female B6C3F1 mice) (NTP 1989) [cited in OECD 2002]. Male and female mice were topically (clipped back skin) administered 12 doses (0, 300, 600, 1200, 2400 or 4800 mg/kg-bw/day) 1,4-benzenediol for 14 days. No clinical signs of toxicity were reported in any treatment group.
Subchronic toxicity	<u>13-week exposure:</u> **Lowest oral NOEL** = 20 mg/kg-bw/day (Sprague-Dawley rats) (Bernard 1988, [cited in OECD 2002]. Rats were administered 0, 20, 64 or 200 mg/kg-bw/day 1,4-benzenediol via gavage for 13 weeks (5 days/week). Tremors and reduced home-cage activity was noted in animals in the 64 and 200 mg/kg-bw/day groups. [Additional studies: NTP 1989].

	Lowest dermal NOAEL = Rats were topically (shaved back skin) administered 0, 2.0, 3.5, or 5.0% (73.9 mg/kg-bw/day in male and 109.6 mg/kg-bw/day in female F344 rats) 1,4-benzenediol for 13 weeks (5 days/week, 6 hr/day). Local effects such as dry skin, brown discoloration of skin or erythema were noted. The NOAEL was established on the basis of no systemic or histopathological effects (David 1994),[cited in OECD 2002].
Reproductive / developmental toxicity	Two-generation reproductive study: Male and female (F0 and F1) Sprague-Dawley sat were administered 1,4-benzenediol via gavage at 15, 50, or 150 mg/kg-bw/day (Blacker et al. 1993). **NOEL** = 15 mg/kg-bw/day (general parental toxicity) **NOEL** = 150 mg/kg-bw/day (reproductive toxicity parental and F1 generation) One F0 male in the 50 mg/kg group developed tremors after dosing. At 150 mg/kg, tremors were observed in several F0 and F1 parental animals of both sexes. Trend analysis showed a significant dose-related decrease in body weight gain in F1 males, but not in F0 males. [Additional information: Krasavage et al. 1992; Bio/dynamics Inc. 1989; Murphy et al. 1992].
Chronic toxicity/ carcinogenicity	Male and female F344 rats were administered 1,4-benzenediol via gavage for 103 weeks (5 times/week)at 0, 25 or 50 mg/kg-bw/day. Interim kill at 15 months (NTP 1989). 15-month interim kill: Rat – chemical-induced nephropathy was seen in males in 25 or 50 mg/kg-bw/day dose groups. Significantly higher relative kidney weight and increased incidence of nephropathy in males and decreased hematocrit, and erythrocyte count (mild regenerative anemia) was noted in females in high dose (50 mg/kg-bw) group. 2-year study: A dose-related increase was noted in renal tubular cell adenomas in male rats after 2-yr exposure. No adenomas were reported in less severe cases of nephropathy or in females. Increased incidence of mononuclear cell leukemia was observed in female rats.
	Male and female B6C3F1 mice were administered 1,4-benzenediol via gavage for 103 weeks (5 times/week) at 0, 50 or 100 mg/kg-bw/day. Interim kill at 15 months (NTP 1989). 15-month interim kill: Elevated relative liver weight in males and females at 100 mg/kg-bw/day. Higher relative brain and kidney weight in females. Compound-related liver lesions were seen in dosed (50 or 100 mg/kg-bw/day) males only. 2-year study: Compound-related increase in the relative liver weights in males (50 or 100 mg/kg-bw/day) and in high-dose females only. Increased incidence of hepatocellular adenomas in dosed female mice only. Follicular cell hyperplasia of thyroid gland seen in dosed male and female mice.
	Male and female F344 rats were administered 1,4-benzenediol via the diet for 104 weeks at 351 or 368 mg/kg-bw/day (Shibata et al. 1991). No mortality or clinical signs of toxicity were seen. In males, higher absolute or relative liver and kidney weight and increased renal tubular hyperplasias and microscopic adenomas were observed in treated animals. Chronic nephropathy was seen in control and treated rats, but more severe in 1,4-benzenediol treated rats.

	In females, absolute or relative kidney weight increased.
	Male and female B6C3F1 mice were administered 1,4-benzenediol via diet for 96 weeks at 1046 or 1486 mg/kg-bw/day (Shibata et al. 1991). No mortality or clinical signs of toxicity were seen. In males, increased incidence of renal tubular hyperplasia and hepatocellular adenoma and liver foci were seen. Hyperplasia of forestomach epithelium was seen in both sexes and increased relative liver and kidney weight was seen in females only. There was evidence of potential carcinogenicity.
Genotoxicity *In vivo*	**Positive:** Chromosomal aberrations, c-mitotic effects, micronuclei and sister chromatid exchanges (bone marrow cells) (Miller and Adler 1989; Xu and Adler 1990; Alder and Kliesch 1990; Pacchierotti et al. 1991) [cited in IPCS 1994; OECD 2002]. 1,4-benzenediol administered via ip route. **Negative:** Dominant lethal mutations (male S-D rats) (Krasavage 1984), [cited in IPCS 1994; IARC 1999]. 1,4-benzenediol given via gavage.
In vitro	**Negative:** Ames assay *S. typhimurium* TA97, 98, 100, 1535, 1537 and 1538. (Haworth et al. 1983; Fahrig 1984; Sakai et al. 1985; Hakura et al. 1996) [cited in IPCS 1994; IARC 1999]. **Positive:** Chromosomal aberrations (Chinese hamster ovary cells), sister chromatid exchange (V79 Chinese hamster cells, human lymphocytes), micronuclei induction (human lymphocytes, Chinese hamster lung cells), DNA damage (HeLa cells) (Morimoto and Wolff 1980; Painter and Howard 1982; Erexson et al. 1985; Galloway et al. 1987; Glatt et al. 1990) [cited in IPCS 1994].

Appendix 4. Overview of reported human health effects for 1,4-benzenediol

Human data is very limited. Ingestion of up to 500 mg/day 1,4-benzenediol over a 20-week period resulted in no observable pathological changes in the blood and urine of human volunteers. Ingestion of large quantities of 1,4-benzenediol may produce tremors, vomiting, convulsions, dyspnoea, cyanosis and coma. Fatalities have been reported after ingestion of 3000–12 000 mg 1,4-benzenediol in photography developing agents (Zeidman and Deuit 1945; IPCS 1994). Dermal exposure to > 5% of 1,4-benzenediol in bleach cream for 3 years caused ochronosis and pigmented colloid milium in South African Black women (Findlay et al. 1975; Findlay and De Beer 1980). A study conducted on 840 male volunteers of different ethnicities showed that 1,4-benzenediol below 3% produced negligible effects on the user's skin (Bentley-Phillips and Bayles 1975). Ochronosis is rare in North America. Abuse of bleaching creams, use of products with higher than labelled concentrations and bleaching agents other than hydroquinone, and use of anti-malarials are some of the factors resulting in higher incidences of ochronosis prior to regulatory changes in Africa (Levit 2006). The IARC (1999) concluded that there is inadequate evidence for carcinogenicity of 1,4-benzendiol in humans. In one cohort study, no significant dose-related changes were seen in the mortality rate or incidence cancer (renal or liver cancer or leukemia) in male or female workers exposed to an average of 0.1 to 6.0 mg/m^3 1,4-benzenediol dust for 8 hr (Pifer et al 1995). In another cohort study, five cases of malignant melanoma observed in lithographers were suggested to have been resulted following exposure to 1,4-benzenediol (Nielsen et al 1996).