Workplace Exposure Standard (WES) review

HYDROQUINONE
(CAS NO: 123-31-9)

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New Zealand Government

WORKSAFE
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appendices

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for hydroquinone should be changed.

It considers the potential for exposures to hydroquinone in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for hydroquinone, which is currently set at a **WES-TWA** of 2**mg/m³** for **inhalable fraction**, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary. Synonyms: 1,4-Benzenediol; Dihydroxybenzene; ρ-Dihydroxybenzene; ρ-Hydroxyphenol; HQ.

2.0 Chemical and physical properties

Hydroquinone is a white, crystalline, odourless solid at room temperature (**ACGIH®**, 2014; **DECOS**, 2012).

The DECOS recommendation on hydroquinone and benzoquinone noted that in aqueous media the two substances can interconvert, depending on pH, via semiquinone (DECOS, 2014).

Chemical and physical properties hydroquinone include:

Molecular weight	110.11g/mol
Formula	$C_6H_6O_2$
Specific gravity	1.332 at 15°C
Melting point	172.3°C
Boiling point	286°C
Vapour pressure	1.33hPa at 132.4°C; 2.4 x 10^{-3}Pa at 25°C
Relative vapour density [air = 1]	3.81
Flash point	Closed cup: 165°C
Auto-ignition	515°C
Log K_{ow}	1.03 at 25°C
Solubility	Water: 9.4g/100mL at 28.5°C; slightly soluble in benzene; soluble in ether; very soluble in ethanol, acetone, carbon tetrachloride
Conversion factors	1mg/m³ = 0.222ppm 1ppm = 4.5mg/m³

ECHA, 2017; ACGIH®, 2014; DECOS, 2012

TABLE 1: Physicochemical properties of hydroquinone

Health-related hazard classifications for hydroquinone:

	HSNO CLASSIFICATION
Substance	Hydroquinone
CAS No.	123-31-9
Classification	6.1B (All); 6.1B (O); 6.3A; 6.5B; 6.6B; 6.9B (All); 6.9B (O); 8.3A

TABLE 2:
HSNO health-related hazard classifications of hydroquinone (**EPA**, 2019)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.
[O] Oral exposure route.
[D] Derman exposure route.
[I] Inhalation exposure route.

3.0
Uses

Hydroquinone is mainly used as a chemical intermediate for hydroquinone-based rubber antioxidants and antiozonants; inhibitors to stabilize monomers; stabilisers for paints, varnishes, motor oils, and fuels, and for antioxidants in the industrial use of fats and oils (DECOS, 2012).

Other uses of hydroquinone include in the photographic industry including black and white photographic film, lithography, and hospital x-ray film, although conversion to digital technology has reduced this demand (DECOS, 2012). A small quantity of hydroquinone is used in cosmetic products, such as depigmenting agents and in oxidative hair dye products (**NICNAS**, 2014).

Hydroquinone occurs in nature as the β-D-glucopyranoside conjugate (arbutin) and as free, unbound hydroquinone resulting in potential exposure via the diet or tobacco products (DECOS, 2012).

Occupational exposure to hydroquinone can occur during production, storage, transportation and end-use.

Workers can be exposed to hydroquinone aerosols [dusts or liquids] via inhalation and eye or dermal contact. Although hydroquinone has a very low vapour pressure it can be oxidised, in the presence of moisture, to benzoquinone that is more volatile [12Pa at 20°C vs hydroquinone: 2.4 x 10^{-3}Pa at 25°C] so a vapour phase is possible (DECOS, 2012).

The number of workers exposed or potentially exposed to hydroquinone in New Zealand workplaces is unknown.

Statistics New Zealand 2019 data indicate that 10,380 New Zealand workers were working in the areas of:

- oil and fat manufacturing
- basic organic chemical manufacturing
- basic polymer manufacturing
- human pharmaceuticals and medicinal product manufacturing
- polymer film and sheet packaging material manufacturing
- rigid and semi-rigid polymer product manufacturing
- paint and coatings manufacturing (NZ.Stat, 2019).

4.0
Health effects

IN THIS SECTION:

4.1 Non-cancer

Humans

The DECOS recommendation on hydroquinone and benzoquinone noted that:

> "Sterner *et al*. (1947; cited in ACGIH 2008) reported that occupational exposure to hydroquinone dust and benzoquinone vapour caused eye irritation, photophobia, lacrimation, and corneal ulceration, with no serious cases appearing from exposures of duration shorter than five years. Benzoquinone was believed to be the chief causative agent, although hydroquinone dust was suspected as a contributory cause. Hydroquinone dust concentrations and benzoquinone vapour concentrations were reported to vary between 1 and 55mg/m^3, and 0.04 and 14mg/m^3, respectively." (References cited in DECOS, 2012).

The New Zealand EPA classifies hydroquinone as a 6.1B substance – a substance that is acutely toxic (EPA, 2019).

The **DFG MAK** Value Documentation on hydroquinone summarised the irritation/corrosion potential in humans:

> "Hydroquinone is used in medicinal preparations as a bleaching agent in the treatment of hypermelanosis and for bleaching the skin of coloured persons. Use of 5% preparations is often accompanied by side effects (dermatosis, erythema, burning). The hyperpigmentation (ochronosis) sometimes occurring after use of bleaching creams containing hydroquinone seems to require the use of more highly concentrated preparations (over 3% hydroquinone) for many years (Davis *et al*. 1990; Howard and Furner 1990; Menke *et al*. 1992; Monti and Peña 1989). After use of 2% preparations, cases of hyperpigmentation or discoloration of the fingernails have been reported only rarely (**NIOSH** 1978).
>
> "Eye damage resulting from exposure to hydroquinone has often been observed in occupational-medical practice. In persons exposed briefly to high concentrations, irritation of the eyes, photophobia, lacrimation and ulceration of the cornea were reported (Grant 1986). After exposure to hydroquinone concentrations of 30mg/m^3 keratitis and discoloration of the cornea occurred (Clayton and Clayton 1981). Slight, reversible eye damage was observed at the workplace if hydroquinone concentrations of 1 to 4mg/m^3 were not exceeded. After exposure to hydroquinone dusts, brown discoloration of the eyes developed within 2 to 3 years. On the cornea, spongy thickening, parenchymal swelling, formation of depressions in the surface, erosion and craters can occur, and sometimes keratoconus. After a further 2 to 3 years the conjunctiva were thick and dry with white and brown spots. After long-term exposure, astigmatism, irregularities of the cornea and a decrease in visual acuity can occur. This damage is not reversible, whereas the pigmentation disappears again after the end of exposure (NIOSH 1978). In one case, parenchymal corneal clouding of both eyes was described 7 years after the end of exposure, after a further 9 years a corneal ulcer developed in one eye (Baader 1961)." (References cited in DFG, 1998).

The New Zealand EPA classifies hydroquinone as a 6.3A substance – a substance that is irritating to the skin (EPA, 2019).

The New Zealand EPA classifies hydroquinone as an 8.3A substance – a substance that is corrosive to ocular tissue (EPA, 2019).

The DECOS recommendation on hydroquinone and benzoquinone summarised the sensitisation potential in humans:

> "Hydroquinone can be considered as a common contact allergen, and sources of non-occupational exposure are for example rubber products in which hydroquinone is present as preservative (Klaassen, 1996). Allergic contact dermatitis represents a delayed (type IV) hypersensitivity reaction (which is distinguished from irritant contact dermatitis).
>
> "Cross-reactions between chemicals may occur if they share similar functional groups critical to the formation of complete allergens (hapten + carrier protein). A cross-reactor of hydroquinone is resorcinol and hydroquinone is a cross-reactor of methyl hydroxybenzoate and phenol (Klaassen, 1996)." (References cited in DECOS, 2012).

The New Zealand EPA classifies hydroquinone as a 6.5B substance – a substance that is a contact sensitiser (EPA, 2019).

The ACGIH® review of hydroquinone summarised the repeated dose toxicity in humans:

> "Sterner *et al*. (1947) reported that the vapor of quinone and dust of hydroquinone, arising during the manufacture of the latter, produced characteristic eye injuries in workers. The injuries developed gradually over a period of years, with no serious cases appearing from exposures of duration shorter than five years. No systemic effects were associated with these injuries. In a companion paper, these same investigators described the exposure levels for quinone vapors and hydroquinone dust. Quinone vapor concentrations taken from various operations in the plant during the period 1943 to 1946 varied from 0.01 to 3ppm. Hydroquinone dust concentrations taken from the packing area varied from 0.2 to 12ppm (Oglesby *et al*., 1947).
>
> "Anderson and Oglesby (1958) found corneal changes consisting of changes in the curvature of the lens, long after exposure had ceased and after the staining and pigmentation of the cornea had disappeared. They concluded that the corneal changes seen were caused by quinone vapor or hydroquinone dust. Naumann (1966) conducted a histopathology study of corneal tissue from three exposed workers. He confirmed the findings of late onset of corneal damage seen by Anderson and Oglesby (1958) and described the histology as stromal degeneration."
>
> "Case reports of occupationally-induced skin depigmentation have been documented in the commercial photography industry and in servicing of photography booths (Frenk and Loi-Zedda, 1980; Kersey and Stevenson, 1981). Vitiligo-like depigmentation was observed on the hands of workers exposed to chemical solutions containing hydroquinone.
>
> "Use of hydroquinone in commercial products used as skin lighteners is considered to be a causal factor for exogenous ochronosis, a skin condition involving the deposition of blue or brownish-blue pigment in the face, neck, back, and extremities (Levin and Maibach, 2001)." (References cited in ACGIH®, 2014).

The New Zealand EPA classifies hydroquinone as a 6.9B substance – a substance that is harmful to human target organs or systems (EPA, 2019).

The ACGIH® review of hydroquinone summarised the genotoxic potential in humans:

> "The clastogenicity of hydroquinone in humans is unclear. Yager *et al*. (1990) studied cultured human lymphocytes from a single individual, concluding that hydroquinone is a major contributor to the aneuploidy observed in the lymphocytes of benzene-exposed workers. Doepket *et al*. (2000), using cultured human lymphocytes from eight individuals, was unable to replicate the results of Yager *et al*. (1990)." (ACGIH®, 2014).

The New Zealand EPA classifies hydroquinone as a 6.6B substance – a substance that is a suspected human mutagen (EPA, 2019).

Animals

The DECOS recommendation on hydroquinone and benzoquinone summarised the acute toxicity in experimental animals:

> "Inhalation **LC_{50}** values are not available.
>
> "The dermal **LD_{50}** value was determined to exceed 1,000**mg/kg bw** in guinea pigs (**OECD**, 1996). The **HSG** (Health and Safety Guide; **IPCS** INCHEM) estimated that the dermal LD_{50} value for hydroquinone may exceed 3,800mg/kg bw in rodents (IPCS INCHEM, 2005).
>
> "Oral LD_{50} values for several animal species ranged between 300 and 1,300mg/kg bw (OECD, 1996; Mollgaard *et al*., 1990) (see also Annex F-3). Acute high-level exposure to hydroquinone caused severe effects on the central nervous system (**CNS**) including hyperexcitability, tremor, convulsions, coma, and death. At sublethal doses, these effects were reversible. According to the OECD hydroquinone is moderately acute toxic via the oral route (OECD, 1996)." (References cited in DECOS, 2012).

The ECHA Substance Evaluation of hydroquinone noted data on an acute inhalation toxicity study with a surrogate substance (isomer of hydroquinone, a structural analogue) that indicated an 8-hour LC_{50} >7.8mg/L (7,800mg/m^3) with no clinical signs (ECHA, 2017).

The DECOS recommendation on hydroquinone and benzoquinone summarised the irritation/corrosion potential in experimental animals:

> "Bleehen *et al*. (1968) observed skin irritation in black guinea pigs after nonocclusive, topical applications of creams containing 5% or 10% hydroquinone, 5 days/week for one month (surface treated not indicated). No irritation was seen at levels of 3% hydroquinone (Bleehen *et al*., 1968).
>
> "In the study of Maibach and Patrick (1989) male and female black guinea pigs were administered hydroquinone in a hydrophilic ointment at concentrations of 0.1, 1.0, and 5.0% via non-occlusive, topical application (surface treated not indicated) for 5 days/week for 13 weeks. The lowest concentration caused marginal irritation, and the medium concentration resulted in a slight to marginal irritation in 30% of the animals (mainly females). Moderate to severe irritation and severe ulcerated inflammatory responses occurred at the highest concentration (Maibach and Patrick 1989, cited in **WHO** 1994)." (References cited in DECOS, 2012).
>
> "Hydroquinone in aqueous solution, for example, in tears, is oxidized by air, forming a brown coloured substance partly due to conversion to benzoquinone (WHO, 1994).

"In a study performed by the Eastman Kodak Company (1971) several crystals of hydroquinone powder were placed into the tight [sic] eye of two rabbits. The treated eye of one animal was washed, while the treated eye of the other animal was unwashed. Irritation was scored at 1, 24, 48h and 14 days after treatment. Slight erythrema of the palpebra developed after 1 h in both washed and unwashed eyes. Eythrema [sic] of the nictitating membrane was also evident in the unwashed eye at 1 h. By 24h, the washed eye appeared normal, but the unwashed eye continued to demonstrate slight erythrema of the palpebra, orbital, and nictitating membranes. Erythrema of the nictitating membranes persisted to 48 h after instillation but was not observed 14 days after treatment (Eastman Kodak Company 1971, cited in OECD 1996).

"In the study of Ferraris de Gaspare (1949), the effect of light on hydroquinone induced eye irritation was studied in rabbits. Hydroquinone (pure substance) was applied daily, for 2-4 months, to the eyes of rabbits which were, respectively, kept in the dark, in sunlight, in normal light, irradiated with **UV** light, or pre-sensitized with haematoporphyrin and then kept under either reduced light or sunlight. Most rabbits developed pigmentation, first in the conjunctiva and then in the cornea. Degenerative alterations of the corneal parenchyma were also observed. Pigment formation appeared earlier in animals exposed to light. Older animals seemed more prone to develop pigment than younger ones. Pigment was deposited in albino rabbit eyes as well as in those of rabbits with normal pigmentation (Ferraris de Gaspare 1949, cited in WHO 1994)." (References cited in DECOS, 2012).

"In guinea pigs, hydroquinone (1–3mg pure substance instilled into the eyes twice daily for 9 weeks) caused immediate but transient irritation. During the second day of application a slight corneal opacity was observed in some animals, and on the third day opacity to varying degrees occurred in most of the animals. Ulcers appeared in two animals. The eyes had fully recovered 3 days after cessation of treatment (WHO, 1994).

"In dogs, hydroquinone (2–5mg pure substance) instilled twice daily (5 days per week for 9 weeks) into the eyes caused immediate but transient irritation and lacrimation. Opacity of the cornea, lacrimation and redness of the conjunctiva were produced within 4 days, but ulcers were not observed. The eyes returned to normal within two days after cessation of treatment (Dreyer 1940, cited in WHO 1994)." (References cited in DECOS, 2012).

The DECOS recommendation on hydroquinone and benzoquinone summarised the depigmentation potential in experimental animals:

"Bleehen *et al*. (1968) reported weak to moderate depigmentation of the skin of black guinea pigs after topical, dermal application of creams containing 1–10% hydroquinone, once daily, five times per week for one month (Bleehen *et al*., 1968). In the study of Jimbow *et al*. (1974), depigmentation in the epilated skin of 24 black guinea pigs (males and females) after topical applications of hydroquinone was observed. Creams containing 2 or 5% hydroquinone in an oil-water emulsion were applied daily, 6 days per week, for 3 weeks. The depigmentation was first seen within 8–10 days and was greatest between 14 and 20 days. It was more marked at the higher concentration. Inflammatory changes and thickening of the epidermis were also reported. When hydroquinone was applied topically for three weeks, biopsy specimens showed that it had caused a marked reduction both in the numbers of melanised melanosomes in the cells and the number of actively functioning melanocytes (Pfeiffer and Metzler, 1996).

> "Depigmentation of the skin was also observed in the study of Maibach and Patrick (1989; study details are outlined in the Section on skin irritation above). At the highest concentration, approximately 40% of the animals dosed showed moderate depigmentation of the skin (females only). At the medium concentration, weak depigmentation was observed in the females (not in males), and at the lowest concentration no depigmentation effects were seen. At the highest concentration, hypopigmentation was noticed in 80–100% of the animals in all dose groups (Maibach and Patrick 1989, cited in WHO 1994)." (References cited in DECOS, 2012).

The DECOS recommendation on hydroquinone and benzoquinone summarised the sensitisation potential in experimental animals:

> "In the study of Rajka and Blohm (1970), the induction and challenge were performed by injecting 0.1ml 0.001% benzoquinone solution. At challenge, 19/20 animals had a positive sensitization reaction. A challenge with 0.001% p-phenylenediamine or hydroquinone after a benzoquinone induction resulted in a positive reaction in 5/20 and 1/20 animals, respectively. After an induction with 0.001% p-phenylenediamine and a challenge with benzoquinone, 16/20 animals were sensitised (Rajka and Blohm, 1970).
>
> "In a guinea pig maximization test performed by Möllgaard *et al*. (1990), the cross-reactivity between p-phenylenediamine and benzoquinone has also been established. However, no data are available on concentrations used and the time schedule for challenge and induction (Möllgaard *et al*., 1990).
>
> "In the study of Basketter and Scholes (1992), the local lymph node assay was compared with the guinea pig maximization test using various compounds among which benzoquinone and hydroquinone. In the maximization test the induction injections were performed with benzoquinone dissolved in 0.09% NaCl aided by acetone if required. For the induction and challenge patch benzoquinone was dissolved in acetone with 30% polyethyleneglycol. The concentrations were 0.005 (injection induction), 10 (induction patch) and 2.5% (challenge patch). All guinea pigs (number not indicated) were sensitized and therefore benzoquinone was classified as "extreme" sensitizer (Basketter and Scholes, 1992). In the local lymph node assay, groups of 4 mice were treated with benzoquinone by a daily topical application of 25µL of a series of concentrations, from 0.5 to 2.5% dissolved in acetone with 20% olive oil on the dorsal surface of each ear for 3 consecutive days. Four to five days after the first topical application, all mice were injected intraveneously [sic] with phosphate buffered saline containing 3H-methylthymidine. After 5 h the mice were killed and the amount of 3H-methylthymidine incorporation in the auricular lymph nodes was assayed. Benzoquinone was positive in this assay (Basketter and Scholes, 1992). Roberts *et al*. (2007) reported a murine **LLNA** threshold (**EC3**) of 0.01% for benzoquinone, classifying it as an extreme dermal sensitizer." (References cited in DECOS, 2012).

The OECD SIDS report on hydroquinone summarised the repeated dose toxicity in experimental animals:

> "Repeated oral dosing caused tremors and reduced activity (≥64mg/kg), reduced body weight gain (≥200mg/kg), convulsions (≥400mg/kg), and nephropathy in F-344 rats (≥100mg/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 (400mg/kg), increased liver weight (≥25mg/kg), and irritation of the forestomach (≥200mg/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 20mg/kg per day.

"Fourteen days of repeated dermal dosing caused reduced body weights of male rats at the 3840mg/kg dose level (6% relative to the controls), but the body weights of female rats at this dose level and of mice at 4800mg/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 (74mg/kg in males and 110mg/kg in females) based on the lack of systemic effects." (OECD SIDS, 2002).

The ACGIH® review of hydroquinone noted that neurotoxic effects were observed in a 13-week gavage study in Sprague-Dawley rats with tremors and depressed locomotor activity in both males and females at 64 or 200mg/kg b.w., but not at 20mg/kg b.w. (Topping *et al*., 2007 cited in ACGIH®, 2014).

The NICNAS review of 1,4-benzenediol summarised the reproductive/developmental toxicity in experimental animals:

"In a two-generation reproductive toxicity study (OECD **TG** 416), male and female SD rats received the chemical orally by gavage at doses of 15, 50 or 150mg/kg bw/d (no details on the timing of exposure). Tremors were observed at the highest dose in several parent rats of both sexes. A single parent male developed tumours at 50mg/kg/day. A parental NOEL of 15mg/kg bw/day and a F1 generation reproductive NOEL of 150mg/kg bw/day were reported (OECD, 2002; Government of Canada, 2008). No adverse effects were observed on survival, reproductive parameters, pup weight, gross lesions or histopathology (**IARC**, 1999).

"In a developmental toxicity study, COBS-CD-BR rats were administered the chemical via oral gavage doses of 30, 100 or 300mg/kg bw/day on gestation days (**GD**) 6-15. There were no observations of malformation, gross variations or skeletal variations (except an increase in the incidence of total common vertebral variations at 300mg/kg bw/day). At the highest dose, slight reductions of mean foetal body weight and maternal body weight gain were reported (IARC, 1999).

"In another study (OECD TG 414), New Zealand White female rabbits were administered the chemical by oral gavage with doses 25–150mg/kg bw/day on GD 6–18. Maternal microphthalmia (small eyes) and decreased maternal weight gain were observed at the highest dose (IARC, 1999). The maternal NOEL was reported to be 25mg/kg bw/d and the NOEL for offspring was 75mg/kg bw/d (OECD, 2002)." (References cited in NICNAS, 2014).

The DECOS recommendation on hydroquinone and benzoquinone summarised the genotoxic potential in experimental animals and *in vitro* test systems:

DNA strand breaks/SCEs

"Hydroquinone induced SCEs *in vitro* in V79 Chinese hamster cells (Glatt *et al*., 1989), in CHO cells either with or without exogenous metabolic activation (**NTP**, 1989), and in human lymphocytes in the absence of metabolic activation. Hydroquinone tested negative in an *in vivo* SCE test using bone marrow cells (IARC, 1999b).

DNA adduct formation

"Covalent binding of hydroquinone to DNA was observed *in vitro* in various cell types (IARC, 1999b). However, covalent DNA binding of hydroquinone could not be demonstrated *in vivo*.

Clastogenic effects

"Hydroquinone tested positive in the *in vitro* micronuclei test in the absence of metabolic activation using embryonic human liver cells, human lymphocytes and V79, IEC-17 and 18 cells (IARC, 1999b; Glatt *et al*., 1989). Chromosome aberrations were induced by hydroquinone *in vitro* in human lymphocytes in the absence of metabolic activation (IARC, 1999b; NTP, 1989).

"The effect of polymorphism of the glutathione S-transferases GST-M1, GSTT1 and GST-P1 on induction of micronuclei (**MN**) and SCEs was studied by *in vitro* hydroquinone treatment of human lymphocytes isolated from healthy volunteers. Hydroquinone induced a significant higher frequency of MN in lymphocytes with the GST-M1 null genotype than with GST-M1 present, while this effect was not seen for SCEs. Additionally, the other polymorphisms did not significantly affect the frequency of MN or SCEs. This suggests that GST-M1 is involved in the metabolic fate of hydroquinone and that polymorphisms in GSTM1 could be related to inter-individual differences in DNA damage arising from the exposure to this compound (do Ceu Silva *et al*., 2004).

"Hydroquinone was *in vivo* weakly positive in the micronucleus test in mouse bone-marrow cells and in mouse liver cells *in utero* (IARC, 1999b). Chromosome aberrations were induced by hydroquinone *in vivo* in mouse bone marrow and spermatocytes/spermatogonia (IARC, 1999b).

DNA mutation

"Hydroquinone was negative in Salmonella strains TA 97, 98, 100, 1535, and 1537, with or without metabolic activation (IARC, 1999b; NTP, 1989). Hydroquinone was mutagenic in Salmonella strains TA102 and TA104 (strains sensitive for oxidative mutagens) (IARC, 1999b). Hydroquinone tested positive for genotoxicity in *S. cerevisiae* without exogenous metabolic activation, and induced gene mutations in mouse lymphoma and Syrian hamster embryo cells in the absence of metabolic activation system (IARC, 1999b). Hydroquinone induced gene mutations in mouse L5178Y/TK lymphoma cells in the presence or absence of metabolic activation (NTP, 1989). Hydroquinone was a potent inducer of gene mutations (6-thioguanine resistance) in V79 cells (Glatt *et al*., 1989).

"No information on *in vivo* induction of gene mutations by hydroquinone was available.

Aneuploidy induction

"Aneuploidy was induced *in vitro* by hydroquinone in Chinese hamster cells, Syrian hamster embryo cells and human lymphocytes, in the absence of metabolic activation (IARC, 1999b).

"Hydroquinone clearly increased the frequencies of hyperploid secondary spermatocytes, which indicated non-disjunction induction during the first meiotic division. Concomitantly, hydroquinone induced meiotic delay in primary and/or secondary spermatocytes (Miller and Adler, 1988).

"Aneuploidy was also induced *in vivo* in mouse bone marrow and spermatocytes (IARC, 1999b).

"Overall, the observations reported above may indicate the potency of hydroquinone to (1) induce DNA strand breaks and SCEs, (2) bind covalently to DNA, (3) induce clastogenic effects both *in vitro* and *in vivo*, (4) induce DNA mutations *in vitro*, and (5) induce aneuploidy both *in vitro* and *in vivo*. It should be noted, however, that generally effects in the *in vitro* tests were seen only at relatively high doses." (References cited in DECOS, 2012).

4.2 Cancer

The International Agency for Research on Cancer [IARC] evaluation of hydroquinone concluded that:

There is *inadequate evidence* in humans for the carcinogenicity of hydroquinone.

There is *limited evidence* in experimental animals for the carcinogenicity of hydroquinone.

With an overall evaluation that:

Hydroquinone is *not classifiable as to its carcinogenicity to humans (Group 3)* (IARC, 1999).

The US National Toxicology Program [NTP] Report on Carcinogens [**RoC**], Fourteenth Edition has no evaluation on the carcinogenic potential of hydroquinone (NTP RoC, 2019).

The New Zealand EPA has not classified hydroquinone as 6.7A or 6.7B substance – substances that are known or presumed, or suspected human carcinogens, respectively.

Humans

The DECOS recommendation on hydroquinone and benzoquinone summarised the carcinogenicity data in exposed humans:

"Friedlander *et al*. (1982) reported a cohort mortality and cancer incidence study of 478 workers (7162 person-years of follow-up) engaged in colour printing and processing at nine laboratories in the continental USA during the period 1964–1976. Six job activities were combined within the processing definition: chemical mix, analytical laboratory, film processing, film take-off, print processing and print take-off, but in only one of these (film processing) was hydroquinone identified as an occupational exposure. A single industrial hygiene measurement of hydroquinone indicated a concentration range and

annual mean time-weighed average of <0.01mg/m^3 air. The control populations were (1) two separate groups of employees with the same company not defined as processors for mortality, and (2) the up-state New York population for cancer incidence. There were 36 deaths (12 from malignancies) observed, giving standardized mortality ratios (**SMR**s) well below 1.0 for all mortalities and about 1.0 for most malignancies. Overall, there were 7 cases of cancer and usually the standardized incidence ratios (**SIR**s) were either below or about 1.0. The only exception was central nervous system tumours, but this was based on just two cases. Given the mixed population observed, only some of whom appear to have been exposed to hydroquinone, and the level of characterisation of exposure to this chemical, it is considered that this study is not informative with regard to the carcinogenicity of hydroquinone (Hutt and Kalf, 1996).

"Pifer *et al*. (1995) reported a cohort mortality study of 879 workers (22,895 person-years of follow-up) at a Tennessee (USA) plant in which hydroquinone was manufactured and used over several decades. Job history records were linked to extensive industrial hygiene data and expertise to estimate cumulative exposure to hydroquinone. Average hydroquinone dust levels ranged from 0.1 to 6.0mg/m^3, with levels over 2mg/m^3 for most of the period of operation of the plant. Mean employment duration was 13.7 years and mean follow-up from first exposure was 26.8 years. Relative risk estimates (SMRs) for this cohort were derived by comparison with the general population of Tennessee as well as with an occupational cohort not exposed to hydroquinone (a plant of the same company, located in New York State). The SMR for all causes of death combined (n=168) was significantly below 1.0, as was the SMR for all cancers combined (n=33). Only two sites, colon (n=5) and lung (n=14) had more than three observed cases. Most site-specific SMRs were well below 1.0. The results were similar for both comparison populations. The dose-response analyses of selected cancer sites did not reveal any meaningful trend of heterogeneity (Pifer *et al*., 1995). The International Agency for Research on Cancer (IARC) noted in 1999 that the numbers of individual cancer sites were small and the power to detect effects was weak, and that this cohort had systematically lower SMRs than the comparison industrial cohort (IARC 1999a).

"Nielsen *et al*. (1996) carried out a cohort incidence study among 837 Danish lithographers born between 1933 and 1942 and registered with the Danish Union of Lithographers in 1947 or later. Questionnaires were sent to cohort members in 1989 to obtain information on job exposures; usable responses were received from 620 workers. About one-quarter of the cohort members reported working regularly with hydroquinone for photographic development. The entire cohort was traced in the Danish Cancer Registry from 1947 to 1989. Relative risk estimates (SIRs) for this cohort were derived by comparison with the general population of Denmark. There were a total of 24 cancers registered, giving an SIR of 0.9. For no site except skin were there more than three cases. Five cases of malignant melanoma occurred, with 1.5 expected (SIR 3.4, 95% confidence interval (**CI**) 1.2–7.5). Among these five, two had reportedly been exposed to photochemicals (such as hydroquinone). In the study it was not possible to distinguish between the carcinogenic effects of the exposure to pigments, dyes, and organic solvents (Nielsen *et al*., 1996). It must be noted that the power to detect effects was weak considering the co-exposure with other photochemicals and the unestablished exposure to hydroquinone of lithographers suffering from malignant melanomas.

"Fryzek *et al*. (2005) reported a retrospective cohort mortality study of 2,624 workers engaged in motion picture film processing at a California (USA) laboratory that is the oldest continuously operating laboratory of this type in the world. All workers were employed for at least 3 months between January 1960 and December 2000. There were 54,462 person-years of follow up with 666 observed deaths (hourly workers, 44,019 person-years with 561 deaths; administrative workers, 10,444 person-years with 105 deaths. Thirty three percent of hourly workers and 19% of administrative workers had worked 10 years or more. The SMR ± **95% CI** for all causes of death combined among hourly and administrative workers, respectively, were 1.1 (1.0–1.2) and 1.1 (0.9–1.3), and for all malignancies combined, 1.0 (0.9–1.2) based on 135 deaths, and 1.2 (0.8–1.7) based on 30 deaths. In most instances the SMRs for individual malignancies were <1.0. Borderline significant excesses of non-Hodgkin lymphoma were observed among hourly workers, SMR = 2.2 (1.0–4.0) based on 10 cases and borderline significant excesses of malignancies of the respiratory system were observed among all workers combined, SMR = 1.3 (1.0–1.6) based on 62 cases. However, there was no exposure-relationship for these malignancies if duration of employment was used as an indicator of exposure. Also no information on cigarette smoking habits of personal was available, so no adjustment for this potential confounder was possible. In the case of non-Hodgkin lymphoma, there was no simple relationship with either duration of employment or year of first employment for hourly workers as a group. As a minimum, 75 chemicals were identified as being used on film production since 1960, including hydroquinone which was used in film development. Only three air sampling data were collected for hydroquinone. One sample was taken before 1981 and was below the detection limit. Two samples taken after 1981 contained 0.014 and 0.052mg/m^3, respectively (Fryzek *et al*., 2005)." (DECOS, 2012).

Animals

The ACGIH® review of hydroquinone summarised the carcinogenicity data in experimental animals:

"There was no evidence for hyperplasia or a significant increase in DNA synthesis in the forestomach epithelium or pyloric gland mucosa in male F344 rats fed 3% hydroquinone for eight weeks (Shibata *et al*., 1990). There was no or only limited influence of dietary (0.8%) hydroquinone on alveolar hyperplasia and esophageal squamous cell carcinomas, respectively, in male F344 rats initiated with methyl-N-amylnitrosamine (Yamaguchi *et al*., 1989).

"The U.S. National Toxicology Program (NTP) conducted 2-year carcinogenicity bioassays of hydroquinone by administering 0, 25, or 50mg/kg of the substance in deionized water by gavage to groups of 65 F344/N rats of each sex, 5 days/week for 2 years (NTP, 1992). Groups of 65 $B_6C_3F_1$ mice of each sex were administered 0, 50, or 100mg/kg on the same schedule. Ten rats and 10 mice from each group were sacrificed after 15 months for an interim evaluation.

"At the 15-month evaluation, the following responses were noted: greater relative kidney weight (high-dose males); decreased hematologic indices (high-dose females); increased severity of nephropathy (male rats); and increased relative liver weights (high-dose male and female mice).

"At termination of the study, body weight changes were unremarkable but were reduced in three of the four high-dose groups. Relative liver weights were increased for dosed male and high-dose female mice. Survival in rats and mice was unaffected. Thyroid gland follicular cell hyperplasia was observed in male and female $B_6C_3F_1$ mice; proliferative lesions were seen in the livers of the male mice. Renal tubular cell adenomas were found in 4 of 55 low-dose and 8 of 55 high-dose male rats as compared to none in vehicle controls. Mononuclear-cell leukemia in female rats occurred with a positive trend, and the incidences in the dosed groups were greater than in the vehicle controls (vehicle control, 9 of 55; low-dose, 15 of 55; high-dose, 22 of 55). (The historical incidence of mononuclear-cell leukemia in water-gavaged vehicle control female F344/N rats was 25%±15%; in untreated controls it was 19%±7%.) There were increased risks in mice for hepatocellular adenomas (Males: vehicle control, 9 of 55; low-dose, 21 out of 55; high-dose 20 of 55. Females: vehicle control, 2 of 55; low-dose, 15 out of 55; high-dose 12 of 55). The NTP report (1992) concluded that the increased incidence of the tumors reported above provided "some evidence" for the carcinogenic activity of hydroquinone. A follow-up histopathology review of the NTP slides suggested that the mechanism of action for the renal tumors may be nongenotoxic (Hard *et al*., 1997)."

"Shibata *et al*. (1991) conducted a 2-year feeding study in male and female F344 rats and $B_6C_3F_1$ mice (plus concurrent controls) fed a diet containing 0.8% hydroquinone for 2 years. There were 30 animals per group. Chronic nephropathy was significantly more severe in male rats than in controls (24 out of 30 in exposed rats: 17 out of 30 in controls). There were also an increase in female rats (8 out of 30 in exposed rats: 1 out of 30 in controls). There were also significant increased risks for renal tubular hyperplasias in male rats (30 out of 30 in exposed rats: 1 out of 30 in controls) and male mice (9 out of 30 in exposed mice: 0 out of 28 in controls). For kidney adenomas, there were significant elevations for male rats (14 out of 30 in exposed rats: 0 out of 30 in controls). There were significant excess risks of liver hypertrophy (26 out of 30 in exposed mice: 0 out of 28 in controls) and hepatocellular adenomas (14 out of 30 in exposed mice: 6 out of 28 in controls) in male mice and significant excess risks for forestomach hyperplasias in male (11 out of 30 in exposed: 1 out of 28 in controls) and female (14 out of 30 in exposed: 3 out of 29 in controls) mice. It has been suggested that these differences between these species are related to differential rates of hydroquinone glucuronidation (Monks and Lau, 1992).

"The renal adenomas in male F344 rats are associated with enhanced cell proliferation in the **P1** and **P2** segments of the proximal tubule and significant elevations in urinary alkaline phosphatase, alanine aminopeptidase, n-acetyl glucosaminidase, other enzymes and glucose were indicative of overt nephrotoxicity; no such changes were observed after similar treatment of female F344 rats or male Sprague-Dawley (SD) rats (English *et al*., 1994a)."

"Lau *et al*. (2001) administered the hydroquinone metabolite, 2,3,5-tris(glutathione-S-yl)HQ (**TGHQ**) intraperitoneally to 40 male Eker rats (plus 40 male sham-treated rats). The original dose in treated animals was 2.5 micromoles/kg for 5 days/week for 4 months. The dose in treated animals was then increased to 3.5 micromoles/kg for an additional 6 months. The results were statistically significant increases in renal tubular lesions (dysplasias, adenomas and carcinomas) in the treated rats compared to the untreated rats. The authors suggested that these tumors arose from renal epithelial cells of the P2/**P3** segment of the renal nephron. These results suggest that TGHQ induces sustained regenerative hyperplasia, loss of tumor suppressor gene function, and the subsequent formation of renal tumors and carcinomas." (ACGIH®, 2014).

The DECOS recommendation on hydroquinone and benzoquinone noted that:

> "Hard and Khan reviewed **CPN** [chronic progressive neuropathy] in 2004 (Hard and Khan, 2004). They argued that CPN is a spontaneous age-related disease that occurs in high incidence in F344 and Sprague-Dawley rats, exhibiting a male predisposition. The disease generally starts at about 2 months of age, when some rats develop basophilic renal tubules with a thickened basement membrane. Progression involves an increase in number of tubules affected, tubular degeneration and atrophy, and an ongoing tubule-cell proliferation. By the time that end-stage is reached, there are virtually no normal tubules remaining and death from renal failure is highly probable. The authors stated that this degenerative and regenerative disease is not the result of any chemical treatment, and it is necessary to distinguish its regenerative aspects from preneoplasia (atypical hyperplasia) from which adenomas develop.
>
> "Furthermore they expressed the opinion that, although the precise etiology of CPN and the mechanisms underlying its pathogenesis remain unknown, evidence is emerging that advanced CPN is a risk factor for a marginal increase in the background incidence of renal tubular tumours. Reviewing the pathological entities associated with chronic renal failure in man, the authors finally concluded that this rodent CPN has no strict human counterpart (Hard and Khan, 2004).
>
> "McGregor (2007) reviewed the human risks of hydroquinone from its carcinogenic and mutagenic properties including the pathology re-evaluation by Hard *et al* (1997). His evaluation showed that all renal tubular adenomas and all cases of renal tubular atypical hyperplasia occurred in areas of severe or end-stage CPN and that the neoplasms were not otherwise confined to any particular part of the kidney. The author proposed and evaluated a non-genotoxic mode of action involving exacerbation of CPN, considering CPN to be a spontaneously occurring rodent renal disease process." (DECOS, 2012).

4.3 Absorption, distribution, metabolism and excretion

The DECOS recommendation on hydroquinone and benzoquinone summarised the **ADME**:

> "Various absorption, distribution, metabolism and excretion studies on hydroquinone were performed in rats. No information is available on kinetics of hydroquinone after inhalation. Hydroquinone absorption via the skin was determined and classified as "slow" (0.5–1**µg/cm²/h**) but may be more rapid with vehicles such as alcohols. After oral administration or intratracheal instillation, hydroquinone was rapidly and extensively absorbed. Distribution was similar for administration via gavage, intravenous injection and intratracheal instillation.
>
> "Hydroquinone can be oxidized via semiquinone to benzoquinone by various enzymes. The reverse reaction can also occur both spontaneously and enzymatically mediated.
>
> "Hydroquinone can be conjugated with sulphate and glucuronic acid resulting in the respective conjugates, which are excreted via the urine. Benzoquinone and semiquinone can also be conjugated with glutathione, resulting in mono-, di-, and tri-glutathione conjugates which are detectable in the bile. The glutathione conjugates can be further metabolised to cysteine conjugates and mercapturic acids.

"The primary route of elimination is via the urine (>85%) in the form of water soluble metabolites. The major urinary metabolites are glucuronide conjugates (45–56%) and sulphate conjugates (19–43%). Mercapturic acids are present at lower levels (<5%). Only a small fraction (about 1–3%) of the urinary metabolites consists of the parent compound." (DECOS, 2012).

The DECOS recommendation on hydroquinone and benzoquinone summarised the mechanistic data for toxicity:

"Hydroquinone can be detoxified by sulphation and glucuronidation. Benzoquinone can be converted to hydroquinone via two-electron reduction by **NQO1** and **NQO2**.

"Redox cycling between hydro- and benzoquinone as well as of their glutathione conjugates can lead to the generation of **ROS**, which potentially causes lipid peroxidation, membrane damage, cytotoxicity, DNA damage, mutagenicity, and carcinogenicity. The cytoprotective mechanisms of the cell (antioxidants, scavenging enzymes, repair processes) counteract the effects of ROS production. The net effect of free radicals on cellular function thus depends on the balance between radical production and the capacity of these cytoprotective systems.

"Benzoquinone, and to a lesser extent hydroquinone, are *in vitro* inhibitors of topoisomerase II, an enzyme responsible for proper chromosome structure and segregation.

"The reactive benzoquinone, the unstable semiquinone and the quinones of their glutathione conjugates are capable of direct covalent binding to macromolecules such as proteins and DNA. This results in protein- and DNA-adducts, and may consequently result in cytotoxicity and/or genotoxicity. The binding of benzoquinone to tubulin may result in the inhibition of microtubule formation.

"DNA-alkylation by benzoquinone (and hydroquinone upon its oxidation to benzoquinone) has been demonstrated *in vitro* only; despite several attempts, the existence of such DNA-adducts *in vivo* has not yet been proven, probably because of extensive biotransformation.

"Mechanistic studies regarding the hydroquinone-induced kidney toxicity showed that the induction of kidney adenomas by hydroquinone is not accompanied by any covalent binding to DNA, but is apparently associated with local cytotoxicity and necrosis in proximal tubular cells, indicating that hydroquinone induced nephrocarcinogenesis is likely linked to increased cell proliferation.

"Overall, the balance of the various metabolic pathways involved, as well as other local physiological conditions (for example, pH) determine the toxicological outcome of exposure to either hydroquinone or benzoquinone." (DECOS, 2012).

5.0 Exposure standards

IN THIS SECTION:

5.1 Other exposure standards

Table 3 below shows hydroquinone exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE	SHORT-TERM LIMIT VALUE
	mg/m³	mg/m³
Australia	2	
Austria	2[1]	4[1]
Belgium	1	
Canada – Ontario	1	
Canada – Québec	2	
Denmark	2	2
Finland	0.5	2[2]
France	2	
Ireland	0.5	
People's Republic of China	1	2[2]
Poland	1	2
Romania	1	2[2]
Singapore	2	
South Korea	2	
Spain[3]	2	
Sweden	0.5	1.5[2]
Switzerland	2[1]	2[1]
USA – NIOSH		2[4]
USA – OSHA	2	
UK	0.5	

TABLE 3: Exposure standards for hydroquinone from around the world

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on hydroquinone were DECOS, ACGIH®, DFG and Safe Work Australia.

[1] Inhalable aerosol.

[2] 15 minutes average value.

[3] "sen".

[4] Ceiling limit value (15 min).

5.2 DECOS

The Dutch Expert Committee on Occupational Standards [DECOS] recommended an **HBROEL** TWA 8 hours for hydroquinone of 4mg/m³ with a "**skin**" notation (DECOS, 2012).

The rationale for their conclusions was:

> "There are no human data on hydroquinone that might justify their use for deriving a health-based occupational exposure limit: studies lack exposure data, exposure is not exclusively to hydroquinone, or the group size is too small." (DECOS, 2012).
>
> "Furthermore the Subcommittee on the Classification of carcinogenic substances concluded that hydroquinone may induce mutations under high exposure conditions, probably due to the formation of ROS. But as long as exposure levels to hydroquinone are below levels inducing local cytotoxicity (and consequently hyperplasia), the risk for carcinogenic effects was considered to be negligible. Based on the available information, the subcommittee was of the opinion that the data are as yet insufficient to evaluate the carcinogenic properties of hydroquinone.
>
> "Based on these conclusions, and the consideration of the Subcommittee on Classification of carcinogenic substances that the carcinogenic mechanism of hydroquinone in animal studies is in all probability a non-stochastic genotoxic mechanism (due to ROS-generation, while inhibition of topoisomerase II may also play a role), the Committee adopts a threshold approach for deriving a HBROEL for hydroquinone." (DECOS, 2012).
>
> "The Committee selected the 2-year mouse carcinogenicity study by NTP as the pivotal one (NTP 1989; Kari *et al*. 1992). In this study a statistically significant increase of the incidence of thyroid hyperplasia was observed in both sexes at 50 and 100mg/kg bw/day, albeit with a serious difference in susceptibility for this effect between males and females. The Committee also took into account the neurotoxic effects with NOAELs of 20 and 15mg/kg bw/day (tremors and reduced home-cage activity at 64mg/kg bw/day in the 13-week rat study of Bernard 1988 (cited in OECD 1996) and Topping 2007, and tremors and decreased body weight at 50mg/kg bw/day in the 2-generation study of Blacker 1993, respectively). However, these neurotoxic effects were mild and of a transient character." (DECOS, 2012).
>
> "The lowest **BMD** and **BMDL** for 10% extra risk are produced by the log-logistic model, with a BMD of 25.1 and BMDL of 15.7mg/kg bw/day. The other models resulted in BMDs varying from 28.5–43.5mg/kg bw/day and BMDLs varying from 19.1–34.0mg/kg bw/day. The Committee considers the BMDL of 15.7mg/kg bw/day the appropriate starting point for the derivation of the HBROEL.
>
> "Since the exposure levels inducing effects in the acute and short term exposure studies are significantly higher than those at in the sub-acute and chronic studies, no elaboration of a Short Term Exposure Limit (**STEL**) or ceiling value for hydroquinone is considered necessary.
>
> "In order to convert this animal BMDL into a HBROEL the following corrections are made:
>
> - correction for the difference in susceptibility for thyroid hyperplasia between male and female mice
> - differences in sensitivity between mice and men
> - route-to-route extrapolation, that is, from the oral to the inhalation route of exposure.

"From the data shown in Table 21 it appears that females are approximately three times as sensitive as males for the thyroid hyperplasia resulting from exposure to hydroquinone. Hence an adjustment factor of 3 is considered appropriate to correct for this difference in susceptibility (there are no data that would justify another factor). The observed BMDL of 15.7mg/kg bw/day is thus adjusted to 5.2mg/kg bw/day.

"With regard to the possible difference in sensitivity between mice and man (that is, both kinetic and dynamic differences) an uncertainty factor of 3 will be used. Applying this results in a value of 1.7mg/kg bw/day.

"Based on the available data it is concluded that oral absorption is nearly complete, and similar for mice and man. It is also assumed, from a precautionary principle view, that absorption by inhalation is 100%. Consequently, an external burden of 1.7mg/kg bw/day will result in an equal internal daily human body burden of (1.7mg/kg bw x 70kg =) 119mg. When this internal dose is divided by the total volume of air inhaled by a human during a working day of 8 hours (10m^3) the adjusted mouse BMDL is converted to an inhalation BMDL in humans of 12mg/m^3.

"For intraspecies differences, that is, to compensate for possible differences in sensitivity among workers, an uncertainty factor of 3 will be used. Taking this last adjustment into account results in a HBROEL for hydroquinone of 12/3mg/m^3 = 4mg/m^3.

"Most occupational exposure limits for hydroquinone of other countries are 2mg/m^3 or lower. In general these are based on its eye and skin irritation properties. But the quantitative data of these properties date from over four decades ago, with exposure data that are not very reliable in view of the then available chemical analytical power. Moreover, there were co-exposures to benzoquinone and aniline which are likely to have influenced negatively the eye and skin irritations observed. Although only limited data are available, the Committee expects that at the level of 4mg/m^3 the risk for eye and skin irritation and sensitization is negligible." (References cited in DECOS, 2012).

"Absorption of hydroquinone through the human skin averaged 1.6, 2.3 and 2.5% per hour of the dose in the first, second and third 4 hours after application of 125µg/cm^2 (see Section 5.1). When 2,000cm^2 human skin would be exposed for 1 hr, the quantity absorbed would be at least 2,000 x 125 x 0.016µg = 4,000µg. In view of the exposure level advised, dermal absorption can add considerably (more than 10%) of the amount taken up via the inhalatory route. For benzoquinone the same way of reasoning is assumed, in absence of experimental data. Therefore the Committee recommends a *skin* notation for hydroquinone and benzoquinone." (DECOS, 2012).

5.3 ACGIH®

The American Conference of Governmental Industrial Hygienists [ACGIH®] review recommended a **TLV-TWA** of 1mg/m^3 for occupational exposure to hydroquinone to minimise the potential for eye irritation and eye damage (ACGIH®, 2014).

The rationale for their conclusions was:

"The related studies of Sterner *et al*. (1947), Oglesby *et al*. (1947), and Anderson and Oglesby (1958) describe eye irritation and characteristic eye lesions in workers exposed to hydroquinone dust. Most of the measured exposures to hydroquinone dust in the above studies were in the range of 1 to 10mg/m^3. Concomitant exposure to quinone vapor makes it difficult to determine precise levels of exposure. Although quinone vapor is more

acutely irritating, hydroquinone dust is thought to stay in contact with the eye for a longer period of time (Oglesby *et al*., 1947). The eye lesions in humans reported in the literature resulted from levels of exposure measured during old hydroquinone manufacturing process involving the oxidation of aniline. NIOSH (1978) recommends that workers exposed to hydroquinone be required to wear eye protection.

"The observations of excess risk of mononuclear-cell leukemia in female rats (NTP, 1992), hepatocellular adenomas in mice (NTP, 1992; Shibata *et al*., 1991), and renal tubular adenomas in male rats (NTP, 1992; Shibata *et al*., 1991), in addition to evidence of clastogenicity (NTP, 1992; Gocke *et al*., 1981; Crebelli *et al*., 1987; Galloway *et al*., 1987; Chatterjee and Sharma, 1972; Tunel *et al*., 1982; Gad-El-Karim *et al*., 1986; Ciranni *et al*., 1988; Adler and Kliesch, 1990; Barale *et al*., 1990; Pacchierotti *et al*., 1991), are consistent with the A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans, notation.

"Available animal and human data on sensitization from exposure to hydroquinone warrant the addition of the **DSEN** notation. Sufficient data were not available to recommend and **RSEN** notation (Basketter and Scholes, 1992; Liden and Boman, 1988; Goodwin *et al*., 1981; Van der Walle *et al*., 1982; Moriearty *et al*., 1978; Liden, 1989; Olumide, 1985).

"Sufficient data do not exist on which to recommend a **TLV-STEL**. Because of slow percutaneous absorption, a **Skin** notation is not designated." (References cited in ACGIH®, 2014).

5.4 DFG

The Deutsche Forschungsgemeinschaft [DFG, German Research Foundation] MAK Value Documentation on hydroquinone concluded that because of its genotoxicity and the results of carcinogenicity studies in animals, hydroquinone should be classified in **Category 3A** [previously Category IIIA] and as such no MAK value could be recommended (DFG, 1998).

The rationale for their conclusions was:

"Hydroquinone is genotoxic. In mammalian cells *in vitro* and *in vivo* it induces micronuclei, chromosomal aberrations, DNA single strand breaks, oxidative damage to DNA and *in vitro* also gene mutations and SCE. In addition it has C-mitotic effects. DNA adducts were detected *in vitro*, adducts in cellular macromolecules also *in vivo*.

"In two well-documented carcinogenicity studies with oral administration of hydroquinone an increase was found in the incidence of hyperplasia and adenomas of the kidneys in male rats and mice; liver adenomas were also detected in the mice. In one study thyroid gland hyperplasia and adenomas, and forestomach hyperplasia occurred in mice, and in another study mononuclear leukaemia was found in female rats. Pathological changes in the blood count and damage to the bone marrow were also variously reported in studies with repeated administration. A cohort study, which, however, is only of limited meaning due to the small number of participants, yielded no evidence of hydroquinone-induced tumours in man.

"Because of its genotoxicity and the results of carcinogenicity studies in animals hydroquinone is classified in Category IIIA2 in the "List of MAK and **BAT** Values". Hydroquinone induces chromosomal aberration and hyperploidy in germ cells of male mice and is therefore classified in Germ cell mutagens group 3.

> "Allergological investigations in man and animals have shown hydroquinone to have sensitizing effects. However, despite the numerous opportunities for exposure, sensitization is rarely observed at the usual maximum concentrations used of 2%. For this reason the substance has provisionally not been designated with an "**S**"." (DFG, 1998).

The DFG MAK Value Documentation on hydroquinone also concluded that hydroquinone should be designated "**H**" for dermal absorption (DFG, 2013).

The rationale for their conclusion was:

> "In the rat, a maximum of 29% of the applied dose (25 or 150mg/kg body weight) was absorbed within 24 hours (Chemical Manufacturers Association 1988 a, see documentation "Hydroquinone" 1998).
>
> "Absorption of the substance through human skin has been demonstrated *in vitro* (Marty *et al*. 1981, see documentation "Hydroquinone" 1998).
>
> "Barber *et al*. (1995) investigated the dermal penetration of hydroquinone in the Franz diffusion chamber. In the experiments both human stratum corneum and full-thickness rat skin were used. Exposure was to 5% aqueous hydroquinone solutions. The rate of absorption for human stratum corneum was 0.52 ± 0.13µg/cm^2 and hour [sic], for rat skin 1.1 ± 0.65µg/cm^2 and [sic] hour. Penetration through human skin was classified as "slow".
>
> "The absorption of relevant amounts of hydroquinone by the skin has been demonstrated in rats and mice. The substance is a known genotoxic carcinogen, for which no tolerable level of exposure can be deduced. It must be assumed, therefore, that even after the percutaneous absorption of small amounts the carcinogenic risk is increased. The substance is therefore designated with an "H"." (References cited in DFG, 2013).

5.5 Safe Work Australia

Safe Work Australia proposed an interim 8-hour TWA of 2mg/m^3 to protect for the risk of irritation of the eye and eye damage in exposed workers (Safe Work Australia, 2019).

Their rationale was:

> "Long-term exposure to Hydroquinone dust at concentrations as low as 1mg/m^3 caused eye injury in workers. No serious injury was identified in workers exposed for less than five years. The main evidence for carcinogenicity is from a two-year oral study in rats and mice that reported excess risks of mononuclear-cell leukaemia in female rats, hepatocellular adenomas in male and female mice, and renal tubular adenomas in male rats (ACGIH, 2018). A cohort of workers with definite and lengthy exposure to hydroquinone had low cancer rates compared with two comparison populations (IARC, 1999). It is confirmed animal carcinogen with unknown relevance to humans (ACGIH, 2018).The weight of evidence from both *in vitro* and *in vivo* studies does not indicate that the chemical is genotoxic (NICNAS, 2014).
>
> Given the limited available data, the current TWA of 2mg/m^3 is recommended to be retained in the interim to limit irritant effects. A priority review is recommended at the next scheduled review to identify additional repeat dose-toxicity and carcinogenicity studies." (Safe Work Australia, 2019).

6.0 Analytical methods for the assessment of airborne zinc oxide

A common method to measure hydroquinone exposure is using NIOSH Method 5004, Issue (NIOSH, 1994).

Using this method, an air sample of 30 to 180L is collected onto a cellulose ester membrane filter using a flow rate of between 1 and 4 litres per minute. On completion of the sample collection, the filter is immediately transferred to a glass container and 10ml of a 1% acetic acid solution is added. The sample is analysed using **HPLC** with UV detection.

The method can achieve a limit of detection of 0.01mg per sample, allowing quantification of airborne hydroquinone concentrations below 0.1mg/m^3.

7.0
Discussion

WorkSafe's WES for hydroquinone has been unchanged since adoption in 1994.

The toxicological database reviewed indicates hydroquinone is locally toxic to humans, causing skin and eye irritation, corneal ulceration, pigmentation/depigmentation and dermal sensitisation; and locally and systemically toxic to laboratory species causing skin and eye irritation, dermal sensitisation, kidney damage, and hepatic and renal tumours.

Based on the aforementioned documentation, informed by the conclusions of the DECOS, Safe Work Australia, ACGIH® and DFG reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 2mg/m^3 for inhalable fraction of hydroquinone to be inadequate to manage health risks from possible workplace exposure:

- Hydroquinone induced liver and kidney tumours in rodents (ACGIH®, 2014).
- Hydroquinone is genotoxic: in mammalian cells *in vitro* and *in vivo* it induces micronuclei, chromosomal aberrations, DNA single strand breaks, oxidative damage to DNA and *in vitro* also gene mutations and SCE; it has C-mitotic effects; and, DNA adducts were detected *in vitro* and cellular macromolecule adducts *in vivo* (DFG, 1998).
- ACGIH® proposed an **OEL** for hydroquinone at 1mg/m^3, based on reports of eye irritation in exposed workers (ACGIH®, 2014).
- The proposed WES-TWA of 1mg/m^3 for hydroquinone is set to be protective against all non-carcinogenic and non-genotoxic endpoints, based on the animal study derived human inhalation BMDL (DECOS, 2012) and reports of eye irritation in exposed workers above 1 to 10mg/m^3 (ACGIH®, 2014).
- A **WES-STEL** is not proposed as the WES-TWA is set, in part, to minimise the potential for eye irritation, and available information is inadequate to recommend a robust WES-STEL.
- The dermal absorption of hydroquinone was categorised as "slow". However, DECOS recommended a skin notation for hydroquinone, based on a calculation that dermal absorption could contribute >10% of body burden relative to inhalation exposure (DECOS, 2012). DFG recommended a skin notation for hydroquinone, based on systemic toxicity in experimental animals after dermal exposure and genotoxic potential (DFG, 2013). A skin notation is justified for hydroquinone, based on calculated potential exposure contribution, reported systemic toxicity after dermal exposure and potential for a simultaneous vapour phase.
- Available information indicates that while hydroquinone is a dermal sensitiser, there is insufficient evidence about respiratory sensitisation (ACGIH®, 2014). Therefore, a ***dsen*** notation is warranted but an ***rsen*** notation is not warranted.

8.0
Recommendations

WorkSafe considers its current WES-TWA of 2mg/m^3 for inhalable fraction of hydroquinone to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. adopt a WES-TWA for hydroquinone of 1mg/m^3 [inhalable fraction]
2. adopt a *skin* notation for hydroquinone, and
3. adopt a *dsen* notation for hydroquinone.

Noting that the recommended WES-TWA of 1mg/m^3 for hydroquinone may not eliminate all risk, due to the possible genotoxic potential of hydroquinone, the impact of dermal absorption, and the potential for dermal sensitisation, so exposures should be minimised.

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
95%CI/$CI_{95\%}$	95% Confidence Interval.
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. Store at: www.acgih.org/store
ADME	Absorption, Distribution, Metabolism and Excretion.
BAT	Biologische Arbeitsstoff-Toleranzwerte [Biological Tolerance Value], a DFG term.
BMD	Bench-Mark Dose.
BMDL	Bench-Mark Dose, lower risk limit.
Carcinogen category 3A	DFG MAK designation: Substances that cause cancer in humans or animals or that are considered to be carcinogenic for humans for which the criteria for classification in Category 4 or 5 are in principle fulfilled. However, the database for these substances is insufficient for the establishment of a MAK or BAT value.
Ceiling or Ceiling Limit Value	Ceiling Limit Value – absolute exposure limit that should not be exceeded at any time.
CI	Confidence Interval.
CNS	Central nervous system.
CPN	Chronic progressive nephropathy.
DECOS	Dutch Expert Committee on Occupational Standards a Committee [DECOS] of the Health Council of the Netherlands. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).
dsen	A substance that can 'sensitise' the skin, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
DSEN	A notation indicating the substance is a dermal sensitiser. DSEN is used in place of SEN when specific evidence of sensitisation by the dermal route is confirmed by human or animal data. An ACGIH® term.
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
DNA	Deoxyribonucleic acid.
EC3	The amount of a substance that is required to elicit a stimulation index of 3 [in a Mouse/Murine Local Lymph Node Assay].
ECHA	The European Chemicals Agency (an agency of the European Union).
EPA	The New Zealand Environmental Protection Authority.
GD	Gestation Day.
"H"	DFG MAK designation: *danger of percutaneous absorption*. Equivalent to the 'skin' notation in the WorkSafe WES special guide.
HBR-OEL/ HBROEL	Health-based recommended exposure limit. European Union term.
HPLC	High performance liquid chromatography.
HSG	Health and Safety Guide, International Programme on Chemical Safety.
HSNO	Hazardous Substances and New Organisms Act 1996, New Zealand.

TERM	MEANING
IARC	International Agency for Research on Cancer, World Health Organization.
IFA	Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung [Institute for Occupational Safety and Health of the German Social Accident Insurance].
Inhalable fraction	Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly <100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009b). (*cf.* Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter)
IPCS	International Programme on Chemical Safety – a World Health Organisation Programme.
LC_{50}	Lethal Concentration 50%: Concentration resulting in 50% mortality.
LD_{50}	Lethal Dose 50%: Dose resulting in 50% mortality.
LLNA	Local lymph node assay.
µg/cm²/h	Micrograms of substance per square centimetre per hour. In the context, rate of dermal absorption per area of exposed skin.
MAK	Maximale Arbeitsplatz-Konzentration, (maximum workplace concentration) is defined as the maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (for example, by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week. A value set by the DFG.
mg	Milligram or one thousandth of a gram.
mg/kg	Milligrams per kilogram.
mg/kg b.w./ mg/kg bw	Milligram of substance per kilogram body weight.
mg/m³	Milligrams of substance per cubic metre of air.
MN	Micronuclei.
NICNAS	National Industrial Chemicals Notification and Assessment Scheme is the Australian government's regulatory body for industrial chemicals.
NIOSH	The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness.
NOAEL	No Observed Adverse Effect Level.
NOEL	No Observed Effect Level
NQO1	NAD(P)H dehydrogenase [quinone] 1.
NQO2	NAD(P)H dehydrogenase, quinone 2.
NTP	National Toxicology Program, US Department of Health and Human Services.
OECD	Organisation for Economic Co-operation and Development.
OEL	Occupational Exposure Limit (equivalent to a WES).
OSHA	Occupational Safety and Health Administration, US Department of Labor.
P1	The beginning and middle portions of the (proximal) convoluted tubule [PCT]of the kidney nephron.
P2	The end portions of the (proximal) convoluted tubule [PCT] and the beginning of the (proximal) straight tubule [PST] of the kidney nephron.
P3	The (proximal) straight tubule [PST] of the kidney nephron, except for the beginning, P2 region.
ppm	Parts of vapour or gas per million parts of air.

TERM	MEANING
RoC/ROC	Report on Carcinogens.
ROS	Reactive Oxygen Species.
rsen	A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
RSEN	A notation indicating the substance is a respiratory sensitiser. RSEN is used in place of SEN when specific evidence of sensitisation by the inhalation route is confirmed by human or animal data. An ACGIH® term.
"S"	Sensitising. A DFG MAK notation.
SCE	Sister Chromatid Exchange.
sen	A substance that can 'sensitise' the skin or respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A term New Zealand also uses.
SIDS	Screening Information DataSet [OECD].
SIR	Standardised Incidence Ratio: the ratio of the observed number of cases to the expected number of cases.
skin	Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A term New Zealand also uses.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
SMR	Standardised Mortality Ratio (SMR) is a measure of the strength or association between exposure and mortality; a form of Relative Risk (RR) in which the outcome is death. The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard). By convention, the figure is usually multiplied by 100 [an SMR of 200 corresponds to a RR of 2.0]. A *value greater than 100/1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017).
STEL	Short-Term Exposure Limit. The STEL is a limit value above which exposure should not occur and usually relates to a 15-minute reference period.
TG	Test Guidelines. An OECD term.
TGHQ	2,3,5-tris(glutathione-S-yl)hydroquinone.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs®
TLV-STEL	TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
UF	Uncertainty factor.
UV	Ultraviolet light.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A New Zealand term.

TERM	MEANING
WES-STEL	The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A New Zealand term.
WHO	World Health Organisation, Geneva.

Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

CLASSIFICATION CODE	MEANING
Acutely toxic	
6.1A	Substances that are acutely toxic – Fatal
6.1B	Substances that are acutely toxic – Fatal
6.1C	Substances that are acutely toxic – Toxic
6.1D	Substances that are acutely toxic – Harmful
6.1E	Substances that are acutely toxic – May be harmful, aspiration hazard
Skin irritant	
6.3A	Substances that are irritating to the skin
6.3B	Substances that are mildly irritating to the skin
Eye irritant	
6.4A	Substances that are irritating to the eye
Sensitisation	
6.5A	Substances that are respiratory sensitisers
6.5B	Substances that are contact sensitisers
Mutagens	
6.6A	Substances that are known or presumed human mutagens
6.6B	Substances that are suspected human mutagens
Carcinogens	
6.7A	Substances that are known or presumed human carcinogens
6.7B	Substances that are suspected human carcinogens
Reproductive/developmental toxicants	
6.8A	Substances that are known or presumed human reproductive or developmental toxicants
6.8B	Substances that are suspected human reproductive or developmental toxicants
6.8C	Substances that produce toxic human reproductive or developmental effects on or via lactation
Target organ toxicants	
6.9A	Substances that are toxic to human target organs or systems
6.9B	Substances that are harmful to human target organs or systems
Skin corrosive	
8.2A	Substances that are corrosive to dermal tissue (UN PGI)
8.2B	Substances that are corrosive to dermal tissue (UN PGII)
8.2C	Substances that are corrosive to dermal tissue (UN PGIII)
Eye corrosive	
8.3A	Substances that are corrosive to ocular tissue

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

Appendix 3: References

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