HEALTH RISK ASSESSMENT:
HYDROQUINONE IN SKIN-LIGHTENING PRODUCTS

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AICIS	Australian Industrial Chemicals Introduction Scheme
bw	Body weight
CAS RN	Chemical Abstract Service Registry Number
CCID	Chemical Classification and Information Database
CIR	Cosmetic Ingredient Review
CMR	Carcinogenic, mutagenic or toxic to reproduction
CNS	Central nervous system
EC	European Commission
ECHA	European Chemicals Agency
EU	European Union
FOB	Functional observational battery
GLP	Good laboratory practice
GPMT	Guinea pig maximisation test
HQ	Hydroquinone
HSNO Act	Hazardous Substances and New Organisms Act 1996
IARC	International Agency for Research on Cancer
INCI	International Nomenclature of Cosmetic Ingredients
IPCS	International Programme on Chemical Safety
IUPAC	International Union of Pure and Applied Chemistry
LD_{50}	Median lethal dose (causes death in 50% of animals)
LLNA	Local lymph node assay
LOAEL	Lowest observed adverse effect level

NIOSH	National Institute of Occupational Safety and Health
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
NZ EPA	New Zealand Environmental Protection Authority
OECD	Organisation for Economic Co-operation and Development
POD	Point of departure
Pow	Octanol-water partition coefficient
PPRTV	Provisional Peer-Reviewed Toxicity Value
p-RfD	Provisional reference dose
SCCS	Scientific Committee on Consumer Safety
SLP	Skin-lightening product
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
UF	Uncertainty factor
UK	United Kingdom
USA	United States of America
US EPA	United States Environmental Protection Agency
US FDA	United States Food and Drug Administration
WHO	World Health Organization
w/w	Weight per weight

EXECUTIVE SUMMARY

The purpose of this report is to summarise generic health risk assessment data for exposure to hydroquinone from the use of skin-lightening products available to consumers both over the counter in physical stores and online. This report will only consider domestic, non-occupational, incidental exposure to hydroquinone.

Skin lightening products, also known as bleaching creams, whiteners, skin brighteners, or fading creams are marketed as treatments for uneven skin tone, acne, age spots, freckles, and wrinkles. For decades, hydroquinone has been used as a bleaching agent in formulations for the treatment of hyperpigmentation.

Formulations with hydroquinone concentrations >5% have been reported to cause local irritation and leukoderma (localised depigmentation) in humans. Continued use of products containing hydroquinone has been reported to cause melanin destruction and exogenous ochronosis (blue-black pigmentation of the skin). Due to these adverse effects, the use of hydroquinone in over-the-counter cosmetic products has been prohibited in many countries, including New Zealand. However, hydroquinone formulations are available as prescription medicines for the treatment of skin disorders associated with hyperpigmentation including melasma, post-inflammatory hyperpigmentation, sunspots, and freckles.

Although the use of hydroquinone is prohibited in cosmetic products, products containing hydroquinone are still available in the market or sold online. However, hydroquinone is often not listed as an ingredient on the labels of these products. This has resulted in product recalls in Europe, the United Kingdom and the United States of America. Creams and lotions were the most common types of products that were recalled. While no information was found on similar product recalls in New Zealand but there have been product recalls for skin-lightening products containing mercury.

Therefore, the highest concentrations of HQ that have been detected in creams (9%) and lotions (10.5%) were used in the risk assessment presented in this report.

The toxicology of hydroquinone is well established in animal studies. The oral and dermal absorption of hydroquinone depends on the exposure concentration, the exposure duration and vehicle. Hydroquinone is rapidly and extensively absorbed in rats following oral administration. However, the rate of absorption through skin is low. Hydroquinone is of low acute toxicity in animal studies by the oral and dermal route of exposure. Hydroquinone is slightly irritating to the skin and causes severe damage to eyes. Repeated dermal exposure of hydroquinone also results in minimal to minor dermal irritation. Repeated oral dosing of hydroquinone has revealed that the kidneys, blood and thyroid gland are the target organs for toxicity in animals.

Hydroquinone has genotoxic potential by the parenteral route of exposure but not through oral exposure. There is limited evidence of carcinogenicity of hydroquinone in experimental animals and it is classified as Group 3 (i.e. not classifiable as to its carcinogenicity to humans) by the International Agency for Cancer Research.

Exposure to hydroquinone occurs through the use of creams and lotions. Creams are generally applied to the face and lotions may be applied to the whole body. In general, dermal exposure is the most important exposure route for creams and lotions, with oral and inhalation exposure not being expected.

Clinical data indicates that the continued use of cosmetic products (at least 1% HQ) can cause melanin destruction and exogenous ochronosis. Hence, the long-term use of SLPs containing HQ at concentrations up to 10.5% also increases the risk of dermal irritation, leukoderma and exogenous ochronosis.

In this assessment, the non-carcinogenic health risks of hydroquinone in creams and lotions through dermal exposure were evaluated by calculating the hazard quotient. The hazard quotient was greater than 1, indicating that the presence of hydroquinone in creams and lotions may be a cause for concern with respect to non-carcinogenic effects. This is consistent with the New Zealand Environmental Protection Authority's current regulatory position, which does not permit hydroquinone to be included as an ingredient in cosmetic products. These findings also suggest that surveillance for the presence of hydroquinone containing SLPs in the New Zealand market may be warranted.

1. INTRODUCTION

The purpose of this report is to summarise generic health risk assessment data for exposure to hydroquinone (HQ) from the use of skin-lightening products (SLPs) that are available over the counter and online to consumers. This report will only consider domestic, non-occupational, incidental exposure to HQ from the use of cosmetic products.

Products classified as medicines that are available through a doctor's prescription are outside the scope of this report.

1.1 CONSUMER PRODUCT DESCRIPTION – SKIN-LIGHTENING PRODUCTS

SLPs, also known as bleaching creams, whiteners, skin brighteners or fading creams, are marketed as treatments for uneven skin tone, acne, age spots, freckles and wrinkles (US FDA, 2024). They are available in the form of creams, lotions, soaps and powders. Historically, SLPs were used by women with dark complexions, but more recently women with fair complexions have also been reported to use them to tone their skin colour (Pahade *et al.*, 2021). This trend has also attracted men and the use of SLPs is becoming popular. The global SLPs market size was valued at USD 10 billion in 2021 and is expected to expand at a compound annual growth rate of 7.5% to top USD 22 billion by 2032 (FactMr, 2024).

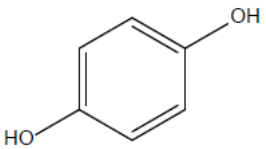
Skin colour is determined by its melanin content. SLPs contain one or more active ingredients that reduce the amount of melanin in the skin where they are applied. This reduces the prominence of skin discolourations and evens out the colour of the skin. HQ and mercury are the most widely used ingredients in SLPs.

HQ has been used as a bleaching agent in formulations for the treatment of hyperpigmentation (Kooyers and Westerhof, 2006). HQ acts by inhibiting the enzyme tyrosinase, which is involved in the production of melanin (Gimeno *et al.*, 2016). The concentration of HQ in commercial SLPs ranges from 1% to 5% (Dermanet, 2024). Formulations with HQ concentrations >5% are reported to cause local irritation and leukoderma (localised depigmentation) in humans. Continued use of products containing at least 1–2% HQ has been reported to lead to melanin destruction and exogenous ochronosis (blue-black pigmentation of the skin) in several ethnic populations (CIR, 2014; Irfan *et al.*, 2022). Adverse effects associated with the over-the-counter use of HQ are most often reported from the inappropriate use of unregulated products containing high concentrations of HQ (Olumide *et al.*, 2008). Due to these adverse effects, the use of HQ in cosmetic products is prohibited in many countries, including New Zealand. However, HQ formulations are available as prescription medicines for the treatment of skin disorders associated with hyperpigmentation, including melasma, post-inflammatory hyperpigmentation, sunspots and freckles.

1.2 PHYSICO-CHEMICAL PROPERTIES OF HYDROQUINONE

HQ is a white crystalline substance when pure and is highly soluble in water (WHO, 1996). HQ is present in many plant materials and is found in tea, coffee, beer, berries, propolis and some mushrooms. Some of the physical and chemical properties of HQ are presented in Table 1.

Table 1. Chemical identification and physico-chemical properties of hydroquinone

Property	Value
INCI name	Hydroquinone
IUPAC name	Benzene-1,4-diol
Other names	Quinol
CAS RN	123-31-9
Chemical structure	
Chemical formula	$C_6H_4(OH)_2$
Molecular weight	110.11 g/mol
Partition coefficient (log Pow)	0.59
Water solubility	70 g/L at 25°C

INCI: International Nomenclature of Cosmetic Ingredients, IUPAC: International Union of Pure and Applied Chemistry, CAS RN: Chemical Abstract Service Registry Number, Pow: octanol-water partition coefficient

1.3 HYDROQUINONE IN COSMETIC PRODUCTS

There are many studies in the literature that have quantified HQ in SLPs. A summary of these studies is presented in Table 2.

Table 2. Concentration of hydroquinone in different skin-lightening products

Cosmetic product	Country	Sample size	Detection method	Mean concentration (range) (%)	Reference
Skin toning creams and cosmetic soaps	Ghana	62	HPLC	(ND–1.6)	(Agorku *et al.*, 2016)
Whitening creams	–	4	RP-HPTLC	0.71	(Alqarni *et al.*, 2021)
Skin-lightening creams	Pakistan	20	HPLC	0.68 (0–7.14)	(Arshad *et al.*, 2021)
Skin-lightening creams	Nigeria	10	UV-spectrophotometry	(2.0–3.3)	(Bamidele *et al.*, 2023)
Herbal cosmetic cream	Thailand	23	HPLC	(2.1–3.3)	(Daodee *et al.*, 2009)
Skin lightening lotions and creams	Nigeria	30	UV-spectrophotometry	0.67 (0–2.35)	(Ekpunobi *et al.*, 2014)
Whitening products	Iran	8	HPLC	(0–0.0015)	(Eradati *et al.*, 2020)
Skin-lightening creams	Canada and West Africa	98	HPLC	1.2 (0–6)	(Gbetoh and Amyot, 2016)
Skin-whitening products	France	95	HPLC	(0.5–9.0)	(Gimeno *et al.*, 2016)
Skin whitening cosmetics	Taiwan	2	RP-HPLC	(3.85–4.00)	(Huang *et al.*, 2004)
Fairness creams	Pakistan	9	HPLC	(0.12–7.2)	(Irfan *et al.*, 2022)
Whitening toner	Indonesia	15	RP-HPLC	Total mean 0.07 (ND–0.36)	(Marumata *et al.*, 2023)
Skin-lightening creams	Nigeria	4	RP-HPLC	(2.58–4.17)	(Osobamiro *et al.*, 2023)
Facial cream and body lotion	India	10	RP-HPLC	(0.08–10.5)	(Pahade *et al.*, 2021)
Skin-whitening cosmetics	Pakistan	22	HPLC	0.024 (0.002–0.10)	(Siddique *et al.*, 2012)
Face-whitening creams	Indonesia	10	UV-Vis spectrophotometry	1.55 (ND–4.77)	(Sirait and Widhihastuti, 2023)
Skin-lightening creams	Nigeria	20	UV-Vis spectrophotometry	(0.07–4)	(Siyaka *et al.*, 2016)
Skin-lightening creams	India	10	UV-Vis spectrophotometry	0.24 (0.006–1.64)	(Zainudin and Azhar, 2022)

HPLC: high-performance liquid chromatography, ND: not detected, RP-HPTLC: reversed-phase high-performance liquid chromatography, UV-Vis: ultraviolet-visible

The majority of the studies summarised in Table 2 were carried out in African and Asian countries where the prevalence of using SLPs has historically been very high (WHO, 2023). Creams and lotions were the most frequently analysed types of products. The highest concentrations of HQ detected in creams and lotions were 9% and 10.5%, respectively.

1.4 REGULATION OF HYDROQUINONE IN COSMETIC PRODUCTS

1.4.1 New Zealand

In New Zealand, cosmetic products are regulated by the New Zealand Environmental Protection Authority (NZ EPA) through the Cosmetic Products Group Standard 2020 under the Hazardous Substances and New Organisms Act 1996 (HSNO Act) (NZ EPA, 2020).

The updated Cosmetic Products Group Standard 2020 that was released in January 2024 listed HQ under Schedule 4 (entry 1339) as a component that cosmetic products must not contain (NZ EPA, 2024). However, HQ can be used in artificial nail systems with a maximum concentration of 0.02% (200 ppm) after mixing for use, by professionals only. The NZ EPA classifies HQ as suspected of causing genetic defects (Muta. 2, H431) (CCID, 2024).

1.4.2 European Union (EU)

HQ is included among the list of substances that are prohibited for use in cosmetic products, listed under entry 1339 of Annex II to Regulation (EC) No 1223/2009. As in New Zealand, HQ is permitted for use by professionals in artificial nail systems with a maximum concentration of 0.02% (200 ppm) after mixing for use. This is the only approved cosmetic use in the EU (Degen, 2016; EC, 2009).

Under the European Cosmetic Products Regulation (No 1223/2009), the use of substances classified as carcinogenic, mutagenic or toxic to reproduction (CMR) under the Classification, Labelling and Packaging Regulation is banned in cosmetic products. According to the harmonised classification and labelling approved by the EU, HQ is suspected of causing genetic defects (Muta. 2, H431) and is suspected of causing cancer (Carc. 2, H351) (ECHA, 2024a).

HQ as an impurity is also restricted in cosmetic products containing alpha- or beta-arbutin (SCCS, 2023). HQ should remain as low as possible in formulations containing alpha- or beta-arbutin and should not be higher than the unavoidable traces in both arbutins.

1.4.3 United States of America (USA)

The cosmetic industry is largely unregulated in the United States of America (USA). The United States Food and Drug Administration (US FDA) has only banned or restricted nine cosmetic ingredients (USFDA, 2024).

It is not clear if HQ is prohibited for use in cosmetics in the USA, but the US FDA does state that “Skin lightening products containing hydroquinone are not approved for over-the-counter sale” (US FDA, 2024).

The Cosmetic Ingredient Review (CIR) is an independent, non-profit scientific body that was established in 1976 to assess the safety of cosmetic ingredients used in the USA. The panel has assessed the safety of HQ on four separate occasions since 1986 and has concluded that:

> “HQ is safe at concentrations of ≤ 1% in cosmetic formulations designed for discontinuous, brief use followed by rinsing from the skin and hair. In addition, HQ is safe for use as a polymerisation inhibitor in nail adhesives and in artificial nail coatings that are cured by LED light. However, HQ is not safe for use in other leave-on cosmetic products”. (CIR, 2014)

This means that HQ should not be used in creams, lotions, serums or moisturisers at any concentration.

1.4.4 Australia

In Australia, cosmetic ingredients are regulated as industrial chemicals under the Industrial Chemicals Act 2019, which is administered by the Australian Industrial Chemicals Introduction Scheme. The use of HQ in cosmetic products in Australia is unclear, and no restrictions or conditions for its use in cosmetic products were found.

The Therapeutic Goods Administration (TGA) regulates medicines and products that are marketed as having a 'therapeutic' effect, including most skin-whitening lotions. Products are determined to be either 'cosmetics' or 'therapeutic goods' based on three factors:

- The primary use of the product.
- The ingredients in the product.
- The claims made about the product.

Therefore, if an SLP (lotion, ointment, cream or soap) makes the therapeutic claim that it inhibits the physiological process of melanin production, it will be regulated as a medicine by the TGA and will be available on prescription only (AICIS, 2023).

HQ is listed in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons [SUSMP]) under Schedule 2 – Pharmacy medicines, Schedule 4 – Prescription only medicines and prescription animal remedies, and Schedule 6 – Chemicals are labelled with poison (Poison Standard, 2024). HQ preparations for human external therapeutic or cosmetic use containing 2% or less of HQ, except in hair preparations containing 0.3% or less of HQ are available through advice from a pharmacist or a licensed person (Schedule 2) or through prescription by a physician (Schedule 4).

1.5 COSMETIC PRODUCT RECALLS DUE TO THE PRESENCE OF HYROQUINONE

Although the use of HQ is prohibited in cosmetic products in the EU and New Zealand, products containing HQ may still be available in the market and sold online. However, HQ is not usually listed as an ingredient on the label of these products. This has resulted in product recalls in Europe, the United Kingdom (UK) and the USA. While no information was found on similar product recalls in New Zealand but there have been product recalls for skin-lightening products containing mercury.

1.5.1 European Union

The European Commission Safety Gate[1] is used by EU market surveillance authorities to notify Member States about unsafe and noncompliant products, including those that present a risk to the health and safety of consumers. The online system serves as a single rapid alert system for dangerous consumer products. All non-food products that are intended for consumers or likely to be used by consumers under reasonably foreseeable conditions are included within the scope of this online system, with the exception of pharmaceutical and medical products.

Michalek *et al.* (2019) summarised SLP violations of the EU regulations that were reported between 2005 and 2018. HQ was identified as one of the major reasons for cosmetic violations (125 of 180 cosmetics) and had an average content of 3.47% of the product weight (range 0.06%–9.60%).

[1] https://ec.europa.eu/safety-gate-alerts/screen/search?resetSearch=true

The Safety Gate alert system contained 56 alerts or recalls for various SLPs due to the presence of HQ between January 2019 and August 2024. The concentration of HQ ranged from 0.01% to 5.4% weight per weight (w/w).

1.5.2 United States of America

The US FDA detected HQ in five SLPs at concentrations ranging from 1.2% to 4.4% from the period 2019-2022 (US FDA, 2022). It is not clear what action was taken by the US FDA in response to this.

1.5.3 United Kingdom

The UK government information website (GOV.UK) contained information on 35 product safety alerts for various SLPs due to the presence of HQ (GOV.UK, 2024), with HQ being detected up to a maximum concentration of 7.8% w/w.

2. HAZARD IDENTIFICATION

2.1 PREVIOUS ASSESSMENTS

No previous health impact assessments that characterised the non-carcinogenic risks of HQ from the use of SLPs were found for New Zealand or other countries.

2.2 HEALTH EFFECTS – INCIDENT SURVEILLANCE AND CASE REPORTS

The use of HQ as a skin-whitening agent became popular in the 1960s after the accidental discovery of its skin-whitening effect on black American workers employed in the rubber industry (Juliano, 2022). SLPs containing HQ can be used over the short term (up to 1–2 months) or long term (from 2 months to 15 years).

Contact dermatitis and exogenous ochronosis are the most common complications from using HQ containing SLPs (Olumide *et al.*, 2008). Ochronosis is the bluish-black discolouration of tissues and has also been observed in people exposed to several other substances in addition to HQ including phenol, trinitrophenol, resorcinol, mercury, picric acid, benzene and antimalarials (CIR, 2010; 2014). It was initially believed that the high concentrations of HQ were the cause of ochronosis, but there have also been reports of ochronosis after the use of 2% HQ preparations. Therefore, duration of exposure is associated with these complications rather than the concentration of HQ.

The long-term use (>6 months) of SLPs containing HQ (at least 1%) is associated with exogenous ochronosis and nail discolouration (CIR, 2010; 2014; Kooyers and Westerhof, 2006; Tan *et al.*, 2008). Ochronosis was reported in South African black women after using strong HQ (>5%) bleaching creams for about 3 years (OECD SIDS, 2002). Charlín *et al.* (2008) also reported four cases of exogenous ochronosis during the treatment of facial melasma with creams containing 2%–6% HQ for 10–20 years, with the skin of each patient initially showing improvement but subsequently exhibiting a worsening of hyperpigmentation. The first, second and fourth patients used relatively low concentrations over a long period of time, while the third patient switched to a higher concentration and noticed intensified darkening of the skin after increasing the concentration of the medicine, indicating that exogenous ochronosis can occur after the use of different concentrations of HQ, with prolonged use being the principle causal factor. Similarly, ochronosis was reported in two Chinese women using skin-whitening creams containing 4% HQ for 5–6 years for the treatment of melasma (Tan *et al.*, 2008). In the first case, the melasma had initially improved with the topical HQ cream but soon deteriorated. Clinical examination revealed mottled, ‘confetti-like’ hyperpigmented macules interspersed between pigmented macules on the cheeks and sides of the face. Histology showed short, stout, curvilinear, ochre-colored fibers of varying thickness in the upper dermis, with solar elastosis. In the second case, hyperpigmentation progressively became darker over a period of 4 years. Histology revealed features identical to those in the first case.

2.3 TOXICOLOGY

The toxicity of HQ is well established in animal studies. Toxicity data have been reviewed and summarised by various authorities, including CIR, the European Chemicals Agency (ECHA) and the National Institute of Occupational Safety and Health (NIOSH), and in various publications (CIR, 2010; 2014; Health Council of the Netherlands, 2015; IARC, 1999; Kooyers and Westerhof, 2006; OECD SIDS, 2002). Consequently, the toxicology of HQ is only briefly summarised below.

2.3.1 Absorption, distribution, metabolism and excretion

The rates of oral and dermal absorption of HQ depend on the exposure concentration, the duration of exposure and the composition of the exposure vehicle Oral and dermal absorption from an alcohol vehicle is greater than from an aqueous solution (CIR, 2010). HQ is rapidly and extensively absorbed (>90%) in rats following oral administration (Matsumoto *et al.*, 2016). However, the rate of absorption through skin is low as compared to oral absorption (ECHA, 2024b; IPCS-INCHEM, 1994).

In a clinical study, volunteers received a single 100 µL dose of radioisotope ^{14}C-HQ (2%) by topical application to 16 cm^2 of forehead skin (125 µg/cm^2*)* for 24 hours (Bucks *et al.*, 1988; Levitt, 2007). Urine was then collected at different time intervals for analysis. The average dermal absorption of HQ estimated from the urinary elimination data was 57%. However, the addition of azone (a penetration enhancer) increased the absorption to 66%, while the addition of Escalol 507 (a sunscreen) with and without azone reduced the absorption of HQ to 35% and 26%, respectively. From these findings, ECHA (2024a) estimated a flux rate of 2 µg/cm^2/hour for human forehead skin based on a dermal dose of 0.125 mg/cm^2 with 40% elimination in the urine within 24 hours.

In vitro assays run in parallel using a 5% aqueous solution of HQ and identical test conditions showed that the human stratum corneum and full-thickness rat skin had similar flux rates (0.524 and 1.09 µg/cm^2/hour, respectively), indicating that there is no major difference in dermal absorption between human and rat skin (Barber *et al.*, 1995; ECHA, 2024b). The absorption rate calculated in this study for humans was about one-sixth of the *in vivo* value reported by (Bucks *et al.*, 1988).

In rats, dermal absorption of HQ was estimated from 10.5% to 11.5% (ECHA, 2024b; Levitt, 2007).

There is no evidence of tissue accumulation of HQ in rats after single or repeated oral dosing (ECHA, 2024b; IPCS-INCHEM, 1994). The amounts of total ^{14}C recovered in tissues and carcasses of Fischer or Sprague-Dawley rats at 24–72 hours following oral application ranged from 0.015% to 1.6%, with the highest amounts being found in the liver (up to 0.6%), indicating that the majority of the dose had been excreted within this timeframe.

The metabolism of HQ is very similar in humans and rodents. The proposed metabolic pathway adapted from IPCS-INCHEM (1994) is depicted in Figure 1. HQ is metabolised mainly by phase II metabolism to sulphate and glucuronide conjugates, with glucuronidation in human liver microsomes being somewhat less than in mouse microsomes but greater than in rat microsomes. A small percentage of HQ can be converted to 1,4-benzoquinone by several cellular enzymes, particularly macrophage peroxidases. In rats that received gavage doses of up to 350 mg/kg, the majority of HQ was recovered as glucuronides (45−53%) and O-sulphate conjugates (19−33%) in the urine, with a small fraction having been metabolised to 1,4-benzoquinone and then to the HQ mercapturate (<5%). 1,4-Benzoquinone is a very reactive metabolite that can be conjugated with glutathione or form DNA adducts (IARC, 1999), and such adducts have been identified in cultures of promyelocytic HL-60 cells (human peripheral blood cells from a leukaemia patient).

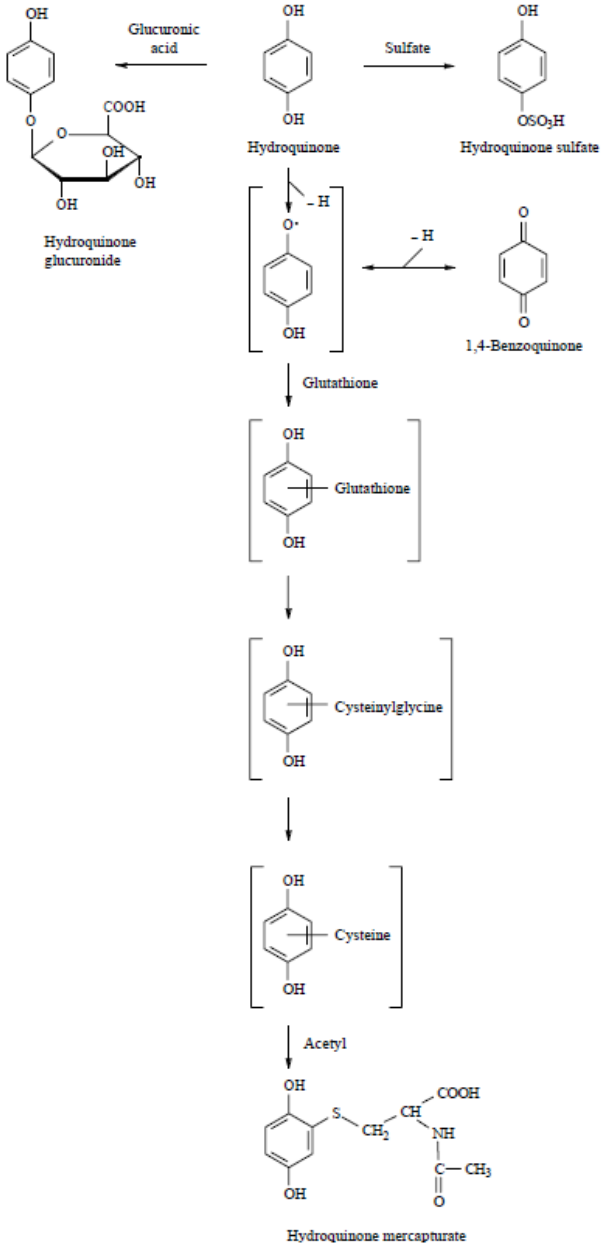


Figure 1. Metabolism of hydroquinone (IPCS-INCHEM, 1994)

HQ is primarily eliminated via the urine (>85%) in the form of hydrophilic metabolites (Health Council of the Netherlands, 2015). The major urinary metabolites are glucuronide conjugates and sulphate conjugates, with mercapturic acids being present at lower levels (<5%). Only a small fraction (about 1–3%) is excreted unchanged in the urine.

2.3.2 Acute toxicity

HQ is of low acute toxicity by the oral and dermal routes of exposure. The acute oral median lethal dose (LD_{50}) in rats is in the range of 290 to 1,000 mg/kg body weight (bw). Signs of acute intoxication are characterised by central nervous system (CNS) stimulation as indicated by tremors observed immediately after dosing and convulsions observed within 5–15 minutes at doses ≥285 mg/kg bw (Topping *et al.*, 2007).

No toxic effects were observed after dermal application of HQ in rabbits at a maximum dose of 2000 mg/kg bw (Topping *et al.*, 2007).

2.3.3 Dermal and ocular effects

No animal studies were available that were performed according to the Organisation for Economic Co-operation and Development (OECD) test guidelines for eye and skin irritation.

Creams containing HQ (1%, 3%, 5%, 7% and 10%) were found to be irritating at concentrations of 5% or more when applied to both bare and non-bare skin of eight black guinea pigs once per day, five times per week for 1 month (IPCS-INCHEM, 1994; OECD SIDS, 2002). Depigmentation was observed in the bare skin of 24 black guinea pigs (both males and females) after the daily topical application of creams containing 2% or 5% HQ on 6 days per week for 3 weeks, and inflammatory changes and thickening of the epidermis were also reported (IPCS-INCHEM, 1994).

No clinical signs of skin irritation by HQ were observed in mice and rats in an acute dermal toxicity study and 14-day dermal toxicity study (NTP, 1989; Topping *et al.*, 2007).

ECHA concluded that HQ is not irritating to skin based on the weight of evidence from an acute dermal toxicity study performed in a way that was comparable to the OECD test guidelines (Topping *et al.*, 2007). ECHA also considered that the findings of two additional studies support this. In the first study, pure HQ did not cause skin irritation in rabbits when applied at doses that were comparable to the OECD requirements, although the test conditions deviated from OECD Test Guideline 404 (ECHA, 2024b). In the second study, no signs of irritation were observed in rats after a 24-hour open dermal application of a 5% or 35% aqueous solution of HQ. The findings in both the studies were reported qualitatively and the severity of dermal effects was not scored.

HQ can cause severe damage to the eyes based on findings in industrial workers (ECHA, 2024b). Acute exposure to high concentrations (not specified) of HQ vapours resulted in eye lesions, irritation, sensitivity to light, lacrimation, injury of the corneal epithelium and corneal ulceration. Chronic exposure to HQ dust led to corneal staining (greenish-brown), corneal opacity and conjunctival staining (brownish to brownish-black), with a distribution corresponding to the palpebral fissure (IPCS-INCHEM, 1994).

Some studies also suggest that powdered HQ causes transient eye irritation and corneal opacity in dogs and guinea pigs and induces slight irritation of the eye in rabbits (IPCS-INCHEM, 1994).

2.3.4 Skin sensitisation

The ability of HQ to induce sensitisation varies from ‘weak’ to ‘strong’ depending on the test procedure and vehicle used. The animal studies summarised were conducted under conditions that were comparable or similar to the current OECD test guidelines.

HQ was found to be a strong sensitiser in the local lymph node assays (LLNA) and guinea pig maximisation tests (GPMTs). In the GPMT, intradermal induction was performed with 2% HQ, followed by a 48-hour occlusive patch with 10% HQ after 7 days (CIR, 2010). A challenge was performed after 14 days using 5% HQ, which showed extreme sensitisation (7/10 animals). Similar results were obtained in another GPMT using an intradermal injection at 2% HQ and topical induction at concentrations of 0.2%, 2.0% or 20% HQ on day 7, followed by an open application challenge with the same concentrations (ECHA, 2024a). By contrast, studies performed at lower HQ concentrations (induction and challenge: 0.001%) have shown a weak sensitisation response (Health Council of the Netherlands, 2015).

HQ also tested positive for skin sensitisation in LLNAs[2] (ECHA, 2024a). However, the sensitisation potential of HQ is highly dependent on the vehicle used in the assay, with EC3 values[3] of 0.08% for acetone, 0.09% for methyl ethyl ketone, 0.15% for acetone/olive oil (4:1), 0.21% for dimethylformamide, 0.35% for dimethyl sulphoxide, and 1–2% for propylene glycol and acetone/physiological saline (1:1).

2.3.5 Subchronic toxicity

The toxicity of HQ after repeated-dose exposure has been investigated in several animal studies and one controlled study on humans. Most of the studies were conducted prior to the establishment of good laboratory practice (GLP) standards, but some of them are comparable to the current OECD test guidelines. The key studies are summarised below.

In the human study, two male volunteers ingested 500 mg of HQ daily for 5 months, and 17 male and female volunteers ingested 300 mg of HQ daily for 3–5 months (IPCS-INCHEM, 1994; OECD SIDS, 2002) correspond to concentrations of 7.1 and 4.3 mg/kg bw/day, assuming an average human body weight of 70 kg. The total daily chemical intake was consumed with meals in three divided doses. Blood samples were analysed for haemoglobin concentration, haematocrit, red blood cell count, differential white blood cell count, sedimentation rate, platelet count, coagulation time and icteric index. Urine was analysed for albumin, reducing sugars, blood cells, casts and urobilinogen. No abnormal findings were reported in the blood or urine. Because the high dose was administered to only two subjects, the low dose (4.3 mg/kg bw/day) was identified as the no observed adverse effect level (NOAEL) for haematological and renal effects in humans. No additional information was reported on the design or results of this study.

No toxic effects were seen in 3 or 14-day dermal toxicity studies conducted at doses up to 3840 mg/kg bw/d for rats and 4800 mg/kg bw/day for mice (Kari *et al.*, 1992; NTP, 1989). Dermal dosing over 13 weeks with 2.0%, 3.5% or 5.0% HQ in an oil-in-water emulsion cream resulted in minimal to minor dermal irritation in rats but no overt toxicity (OECD SIDS, 2002). No compound-related effects occurred in organ weight, clinical pathology or histopathology.

Repeated oral dosing of HQ caused tremors, reduced activity, reduced body weight gain and convulsions in experimental studies, as well as nephropathy in F344/N rats.

In 13-week studies conducted by the National Toxicology Program (NTP), F344/N rats and B6C3F1 mice received HQ (0, 25, 50, 100, 200, or 400 mg/kg bw/day in corn oil by gavage 5 days per week (Kari *et al.*, 1992; NTP, 1989).

Rats: All the rats died at highest dose and 3/10 female rats at 200 mg/kg bw/day died before the end of the study. Tremors and convulsions were also observed in most of the rats that received 400 mg/kg bw/day and in several female rats receiving 200 mg/kg bw/day. The mean body weights of vehicle control and dosed female rats in all groups were similar. In females, the absolute and relative liver weight increased significantly in the 50 mg/kg bw/day and higher dose groups and showed a dose-response relationship. By contrast, in males, the absolute and relative liver weights decreased significantly in the 25, 50, 100 and 200 mg/kg bw/day dose groups, increasing only in the highest dose group and showing no dose-response relationship. Inflammation and/or epithelial hyperplasia (of mild to moderate severity) of the forestomach was seen in both male (4/10) and female rats (1/10) at a dose of 200 mg/kg bw/day but not at the other doses. Toxic nephropathy characterised by tubular cell degeneration in the renal cortex was also seen in both male (7/10) and female rats (6/10) that

[2] Sensitisers induce proliferation of lymphocytes in the lymph nodes draining the site of test substance application. The level of proliferation is proportional to the dose and to the potency of the applied allergen. The ratio of the mean proliferation in each treated group to that in the concurrent control group, (known as the Stimulation Index), which should be ≥3.

[3] The EC3 value is the concentration of chemical required to induce a three-fold increase in lymph node cell proliferation.

received 200 mg/kg bw/day and in females (1/10) that received 100 mg/kg bw/day. The kidney lesions in male rats were judged to be of moderate to marked severity, while those in female rats were similar but of lesser (minimal to mild) severity. No renal lesions were observed in rats of either sex at 50 mg/kg bw/day. The NOAEL for this study was 50 mg/kg bw/day based on kidney lesions being observed in females and a decreased body weight being observed in males at 100 mg/kg bw/day, which was considered the lowest observed adverse effect level (LOAEL).

Mice: mortality was observed at 200 mg/kg bw/day (2/10 males) and 400 mg/kg bw/day (8/10 males and 8/10 females) (Kari *et al.*, 1992; NTP, 1989). Mean body weights were similar in all test groups and vehicle group. Lethargy was the most common clinical sign observed in all males and females (from 100 mg/kg bw/day). Tremors were observed after dosing and convulsions preceded death in both sexes at 400 mg/kg/ bw/d and in males at 200 mg/kg/ bw/day. The absolute and relative liver weights increased significantly in all male and in female mice at 100, 400 and 200, 400 mg/kg bw/day compared with the vehicle control group. However, the changes in liver weights are considered of no toxicological significance as the effects did not show a clear dose response and were observed in the absence of corresponding histopathological findings. Ulceration, inflammation or epithelial hyperplasia of the forestomach was observed in male (3/10) and female (2/10) mice at 400 mg/kg bw/day and in females (1/10) at 200 mg/kg bw/d. HQ doses of 100 mg/kg bw/d and below resulted in no toxicity l. Renal lesions were not observed in mice at any dose level. The NOAEL for this study was 100 mg/kg bw/day based on marked tremors or convulsions being observed at 200 mg/kg bw/day.

A more recent subchronic toxicity study by Topping *et al.* (2007) was conducted in accordance with GLP and the study protocol was comparable to OECD Guideline 424 for neurotoxicity testing. In this study, there was no evidence of subchronic neurotoxicity after oral exposure to HQ (99% pure) in Sprague-Dawley rats (10/sex/group) at doses of 0, 20, 64 and 200 mg HQ/kg bw/day administered by gavage, 5 days per week for 13 weeks. Adverse effects on the CNS, including tremors and reduced activity, were observed at doses of 64 and 200 mg/kg bw/day. Tremors were transient, occurred within 1 hour of dosing and resolved by the 6-hour examination. These neurological effects appear to be acute, as recovery occurred prior to subsequent functional observational battery (FOB) observations. The nephrotoxic effects observed by Kari *et al.* (1992) in F344/N rats after HQ exposure were not observed in this study with Sprague-Dawley rats. As renal effects were also not seen in the NTP's 13-week mouse study, these effects may be both species and strain specific. Under the conditions of this study, the LOAEL in Sprague-Dawley rats was 64 mg/kg bw/day based on clinical signs indicating an acute adverse effect on the CNS, and the NOAEL was 20 mg/kg bw/day.

2.3.6 Genotoxicity

The genotoxic effects of HQ have been studied extensively in a wide range of *in vitro* and *in vivo* studies, but the results have been highly dependent on the route of exposure (ECHA, 2024b; IPCS-INCHEM, 1994). Both the *in vitro* and *in vivo* studies were comparable or similar to the OECD test guidelines.

In vitro studies

HQ is not mutagenic according to the Ames test, with negative results having been reported with various strains of *Salmonella typhimurium* (TA97, TA98, TA100, TA1535, TA1537 and TA1538) and *Escherichia coli*, with or without metabolic activation (ECHA, 2024b). However, positive results have occasionally been reported in reverse mutation assays with a single strain (TA1535A) of *S. typhimurium* using a non-standard incubation medium and without metabolic activation.

In vitro studies with various cell lines have shown that HQ is capable of inducing gene mutations, structural chromosome aberrations, sister chromatid exchange and DNA damage.

In vivo studies

HQ induced structural chromosome aberrations and c-mitotic effects *in vivo* in mouse bone marrow cells following intraperitoneal injection (IPCS-INCHEM, 1994; OECD SIDS, 2002). HQ also produced a weak but significant induction of micronuclei in the bone marrow of animals treated by gavage but did not have this effect when administered in the diet. HQ produces adducts with DNA *in vitro*, but recent *in vivo* studies (comet assay in rats, transgenic rodent mutation assay) were unable to replicate this (ECHA, 2024b). In addition, no evidence of mutagenicity was demonstrated in an *in vivo* mouse spot test and in a dominant lethal assay in male rats treated with HQ at oral doses of 30, 100 or 300 mg/kg bw/day for 10 weeks.

In vitro genotoxicity studies are frequently, but not always, positive, while *in vivo* studies are typically negative unless detoxication pathways are overcome by parenteral administration. Overall, HQ has shown mutagenic effects, but the human relevance of these effects remains uncertain. The exposure route in all of the *in vivo* studies reporting positive effects was parenteral, which is not relevant to human exposure. Based on these observations, ECHA classified HQ as "Germ cell mutagenicity category 2, H341 suspected of causing genetic effects", but only through intraperitoneal application or *in vitro* (ECHA, 2024b). Therefore, the risk of genetic effects after oral or dermal exposure is very low.

2.3.7 Chronic toxicity/carcinogenicity

Epidemiological studies in HQ-exposed workers suggest that kidneys, livers, or blood system are not the specific target organs of a possible carcinogenic effect of HQ, even at the elevated exposure levels of the early years of HQ production before 1950 (ECHA, 2024b; IARC, 1999; US EPA, 2009). There was no evidence of excess mortality in the investigated cohorts. Cases of reported malignant kidney tumours were confounded by an excessive smoking history, which is recognised as major cause of renal cancer in humans, and by workplace exposure to other chemicals.

There are two key studies that assessed the carcinogenicity potential of HQ. One study was conducted by the NTP (Kari *et al.*, 1992) and the second by Shibata *et al.* (1991) in F344/N rats and B6C3F1 mice. These studies and a review of their findings by IARC (1999) are summarised below.

Kari et al. *(1992)*

The study protocol used by the NTP was similar to OECD Guideline 453 for combined chronic toxicity/carcinogenicity studies. However, there were some deviations, such as including only two instead of the recommended three dose groups, and not reporting on food consumption or urinalysis.

In the NTP study, F344/N rats (65/sex/group) received HQ at doses of 0, 25 or 50 mg/kg bw/day by gavage in deionised water for 5 days/week for up to 103 weeks (Kari *et al.*, 1992). B6C3F1 mice (65/sex/group) were similarly exposed to HQ at doses of 0, 50 or 100 mg/kg bw/day on the same schedule.

No substance-related clinical signs of toxicity were observed in rats. Spontaneous nephropathy was observed in all male and most of the female rats exposed to HQ and in the vehicle control group. Nephropathy was characterised by varied degrees of degeneration and regeneration of tubular epithelium, atrophy and dilatation of some tubules, hyaline casts in the tubular lumina, glomerulosclerosis, interstitial fibrosis, and chronic inflammation. The nephropathic changes occurred in animals sacrificed at both 15-month and 2-year intervals were consistent with age-related advanced renal disease but were more severe in males that

received 50 mg/kg bw/day than in the control group. Significant decreases in the red blood cell count, haematocrit percent and haemoglobin concentration (at 15 months) were observed in females in the 50 mg/kg bw/day dose group compared with the control group. The NOAEL for general toxicity was 25 mg/kg bw/day based on haematological changes in females and the increased severity of toxic nephropathy and reduced body weight in males at 50 mg/kg bw/day.

The incidences of neoplastic lesions observed in rats after 103 weeks are presented in Table 3. In males, the incidence of renal tumours was significantly positively related to HQ dose and was significantly higher in the high-dose group than in paired controls. Furthermore, the incidence of renal tumours in both dose groups exceeded the highest historical incidence of this tumour type in both untreated (6%) and water gavage treated (2%) controls and was markedly higher than the overall historical incidence in both types of controls (<0.05%). In females, the incidence of mononuclear cell leukaemia was significantly positively related to dose and was significantly higher in the high-dose group than in paired controls, albeit still within the historical control range (25% ± 15%). The severity of the observed leukaemia was also higher in the high-dose group than in the paired controls.

Table 3. Incidences of neoplastic lesions in F344/N rats treated with hydroquinone (Kari *et al.*, 1992)

Tumour type	Dose (mg/kg bw/day)		
	0	25	50
Males			
Renal tubule cell adenoma	0/55[s] (0%)	4/55 (7%)	8/55[b] (14%)
Females			
Mononuclear cell leukaemia	9/55[b] (16%)	15/55 (27%)	22/55[c] (40%)

bw: body weight

[s] $p \leq 0.005$ by logistic regression trend test.

[b] $p \leq 0.005$ by logistic regression pairwise test.

[c] $p \leq 0.01$ by logistic regression pairwise test.

In the mouse study, no HQ-related clinical signs or effects on survival were observed. The lethargy observed in the 13-week mouse study was not observed in the chronic study, making the relevance of this effect questionable. However, the relative liver weights of male and female mice in the high-dose group that were killed at 15 months were significantly greater than those of the vehicle control group.

There was some evidence of carcinogenic activity of HQ in the female mice, as shown by increases in liver hepatocellular neoplasms, mainly adenomas. The neoplastic lesions observed are presented in Table 4.

Table 4. Incidences of neoplastic lesions in mice treated with hydroquinone (Kari *et al.*, 1992)

Tumour type	Dose (mg/kg bw/day)		
	0	50	100
Males			
Hepatocellular adenoma	9/55[b]	21/54[c]	20/55[d]
Hepatocellular carcinoma	13/55	11/54	7/55
Hepatocellular adenoma or carcinoma	20/55 (36%)	29/54 (54%)	25/55 (45%)
Females			
Hepatocellular adenoma	2/55[e]	15/55[f]	12/55[f]
Hepatocellular carcinoma	1/55	1/55	1/55
Hepatocellular adenoma or carcinoma	3/55[d] (5%)	16/55[e] (29%)	13/55[e] (24%)

bw: body weight

[b] $p < 0.05$ by logistic regression trend test.

[c] $p < 0.01$ by logistic regression pairwise test.

[d] $p < 0.05$ by logistic regression pairwise test.

[e] $p < 0.01$ by logistic regression trend test.

[f] $p < 0.005$ by logistic regression pairwise test.

In both dose groups of males, significant increase in the incidences of hepatocellular adenomas and carcinomas was observed but without a dose response relationship. The increased incidences of hepatocellular adenomas were offset by decreased incidences of hepatocellular carcinomas so that the combined incidences of hepatocellular adenomas or carcinomas were not significantly different from the vehicle control group (US EPA, 2009). Historical incidences for combined liver tumours in untreated and water gavage controls averaged 30%, but ranged as high as 58%, for male mice. Although, in both dose groups, the incidence of liver adenomas showed a similar, statistically significant increase in adenomas, the incidence of liver carcinomas was lower than in the vehicle controls (ECHA, 2024a). The combined incidences of hepatocellular adenomas or carcinomas in the female mice were significantly elevated in both treated groups but without a dose response relationship. The incidence of combined liver tumours in both dose groups in females exceeded the historical range for untreated (9.1 ± 4.7%, max = 20%) or water gavage (8.3 ± 5.0%, max = 14%) controls.

Shibata et al. *(1991)*

Shibata *et al.* (1991) only tested one dose of HQ (0.8%) in F344/N rats (equivalent to 351 and 368 mg/kg bw/day for males and females, respectively) and B6C3F1 mice (equivalent to 1,046 and 1,486 mg/kg bw/day for males and females, respectively), so it was not possible to make any conclusions concerning possible dose-response relationship.

Chronic nephropathy was observed in all rats but was more severe in males that were given 0.8% HQ. The incidences of tubule hyperplasia and adenomas in the kidneys of male rats were 30/30 (100%) and 14/30 (47%), respectively, in the treated group, which were significantly higher than the respective controls (1/30 [3%] and 0/30 [0%], respectively; $p < 0.01$). Tubule adenomas were the only tumour type with an increased incidence over the controls. In females, tubule hyperplasia was observed in only two female rats. No other treatment effects were observed in the kidneys of female rats.

In the mouse study, the combined incidence of hepatocellular adenomas or carcinomas in male mice was 20/30 in the dosed animals ($p<0.05$) compared with 13/28 in the control animals

IARC (1999)

In its review of the studies of Kari *et al.* (1992) and Shibata *et al.* (1991), IARC (1999) noted that the incidence of leukaemia in the exposed female rats was within the historical control range. Additionally, it noted that the increase in kidney tumours entirely concerned adenomas (i.e. none of these studies adenocarcinomas were observed). It was also noted that despite the same B6C3F1 mouse strain being used in both studies, Kari *et al.* (1992) observed an increased incidence of liver tumours in females but not males, while Shibata *et al.* (1991) found an increased effect in males without any effect in females.

IARC (1999) concluded that there is *limited evidence* in experimental animals of the carcinogenicity of HQ and classified it as Group 3 (i.e. not classifiable as to its carcinogenicity to humans).

2.3.8 Developmental and reproductive toxicity

Developmental and reproductive toxicity studies have been conducted according to the OECD test guidelines.

Developmental toxicity studies with rabbits and rats did not show any treatment-related effects on foetal development (ECHA, 2024b; Health Council of the Netherlands, 2015; IARC, 1999). In a developmental toxicity study in New Zealand rabbits, treatment with HQ at 150 mg/kg bw/day produced minimal developmental alterations (incidences of ocular and minor skeletal malformations) in the presence of maternal toxicity. In another study, the NOAEL for both maternal and developmental toxicity was 100 mg/kg bw/day, and the LOAEL (maternal and developmental) was 300 mg/kg bw/day.

In a two-generation reproductive toxicity study in rats, no adverse effects were observed on feed consumption, survival, reproductive parameters, pup weight, sex distribution, survival, gross lesions or microscopic anatomy of the offspring after oral doses of HQ of 15–150 mg/kg bw/day (ECHA, 2024b; Health Council of the Netherlands, 2015; IARC, 1999). However, mild and transient tremors were observed in one male rat at 50 mg/kg bw/day and in several males and females at 150 mg/kg bw/day.

These findings indicate that HQ has no developmental or reproductive toxicity potential.

2.3.9 Toxicology summary

The toxicology of HQ shows that a wide range of effects are observed in animals and are species specific. The kidneys, blood and thyroid gland being the target organs. Haematological changes and kidney lesions are specific to rats only, while the thyroid gland was also a target for HQ toxicity in mice. Effects on the CNS are observed in both rats and mice but are transient and considered acute. HQ has genotoxic potential by the parenteral route of exposure but not through oral exposure. There is limited evidence of carcinogenicity of HQ in experimental animals and it is classified as Group 3 (i.e. not classifiable as to its carcinogenicity to humans) by IARC.

3. DOSE-RESPONSE INFORMATION

In this section, concerns associated with exposure to HQ in SLPs are considered in relation to subchronic and chronic exposure.

The points of departure (PODs) from the subchronic and chronic toxicity studies summarised in section 2 are presented in Table 5.

Table 5. Points of departure for non-carcinogenic effects of hydroquinone

Study	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Key effects	Reference
Subchronic oral toxicity study (3–5 months) – humans	4.3	–	No dose-related haematological or renal effects	(IPCS-INCHEM, 1994)
Subchronic oral toxicity study – rats	50	100	Kidney lesions in females and 8−9% reduction in body weight in males	(Kari *et al.*, 1992)
Subchronic oral toxicity study – mice	100	200	Gastric histopathology, tremors and death	(Kari *et al.*, 1992)
Subchronic oral neurotoxicity study – rats	20	64	Acute neurological effects (tremors, convulsions)	(Topping *et al.*, 2007)
Chronic oral toxicity study – rats	25	50	Haematological changes in females and an increased severity of toxic nephropathy and reduced body weight in males	(Kari *et al.*, 1992)
Chronic oral toxicity study – mice	–	50	Incidences of thyroid follicular cell hyperplasia at 65-week interim sacrifice	(Kari *et al.*, 1992)
Chronic oral toxicity study – rats	688	–	No dose-related effects	(IPCS-INCHEM, 1994)

NOAEL: no observed adverse effect level, bw: body weight, LOAEL: lowest observed adverse effect level

From Table 5, it is evident that the PODs from subchronic and chronic toxicity studies in rats are in a similar range and rats appear to be more sensitive to HQ than mice. In Sprague-Dawley rats, CNS effects were observed from the dose of 64 mg/kg bw/day (Topping *et al.*, 2007), while no CNS effects were observed at 50 mg/kg bw/day and below, even in chronic studies combined with assessments of carcinogenicity (Kari *et al.*, 1992). Hence, it can be inferred that CNS effects do not occur at or below a dose of 25 mg/kg bw/day. The CNS

effects in rats occurred within 1 hour after dosing and were therefore acute effects (Topping *et al.*, 2007), so the POD from this study was not considered in the risk assessment.

Provisional Peer-Reviewed Toxicity Values (PPRTVs) may be derived for situation-specific risk assessments (US EPA, 2009). PPRTVs differ from the US EPA's reference dose (RfD) in that PPRTVs do not receive the multiprogramme consensus review provided for RfDs. For HQ, PPRTV in the form of a provisional reference dose (p-RfD), was established by the US EPA (US EPA, 2009).

The US EPA reviewed all the studies and selected a POD from a clinical study. The subchronic NOAEL for haematological and renal effects in humans (4.3 mg/kg bw/d) was also the lowest NOAEL of the studies summarised in Table 5.

$$\text{Chronic pRfD} = \frac{4.3\ \text{mg/kg bw/day}}{100} = \mathbf{0.04\ mg/kg\ bw/day}$$

The oral absorption of HQ is extensive and rapid (>90%), so the oral external dose (NOAEL) can be considered equivalent to the oral systemic dose. The US EPA derived a chronic p-RfD by applying an uncertainty factor (UF) of 100 (US EPA, 2009). An UF of 10 is applied to account for variation in human sensitivity; and an UF of 10 is applied for extrapolation from subchronic to chronic exposure.

4. EXPOSURE ASSESSMENT

As previously discussed, HQ is prohibited in products that are available over the counter to consumers. However, HQ-containing products are available on prescription for medical conditions. It is unknown what concentrations of HQ may be present in SLPs that are available to New Zealanders through other retail channels, so the maximum concentrations for creams and lotions provided in Table 2 (9% and 10.5%, respectively) were used in the current assessment to estimate exposure to HQ from the use of these products.

4.1.1 Exposure models (Tier 1 approach)

Risk assessment may follow a tiered approach. Under a tiered approach, initial exposure estimates are derived using highly conservative assumptions. If such estimates indicate no cause for concern, then more refined approaches are unnecessary.

Tier 1 assessment is usually used to screen consumer exposure based on the summation of high-percentile product use levels and maximum concentrations of the substance of interest in products to give a worst-case exposure scenario. Due to the lack of data on a number of inputs to the exposure assessment, a Tier 1 approach was used in the current situation.

4.1.2 Dermal exposure

SLPs are most commonly applied to the face, but lotions may be applied to the whole body. Therefore, scenarios were developed for the use of SLPs on both the face and the whole body. Dermal exposure occurs when a chemical crosses the dermal barrier and enters the portal circulation. The amount of chemical absorbed will depend on its concentration in the external medium, the duration and frequency of exposure to the external medium, and the characteristics of the chemical, as well as the proportion of the skin surface that contacts the external medium.

Compounds that come in contact with the skin are potentially subject to three processes.

- Evaporation from the skin surface.
- Uptake into the stratum corneum, followed by reversible or irreversible binding.
- Penetration into the viable epidermis, followed by metabolism.

In the case of SLPs, the concentration of HQ contacting the skin will decrease as it is absorbed. However, the rate of absorption is likely to be sufficiently low that the concentration of HQ contacting the skin can be considered to remain constant. Therefore, dermal exposure will be dependent on the contact time.

The dermally absorbed dose (DAD; mg/kg bw/day) is calculated as:

$$\mathrm{DAD} = \frac{\mathrm{DA_{event}} \times \mathrm{EV} \times \mathrm{ED} \times \mathrm{EF} \times \mathrm{SA}}{\mathrm{BW} \times \mathrm{AT}}$$

where DA_{event} is the absorbed dose per event (mg/cm^2/event), EV is the event frequency (events/day), ED is the exposure duration (years), EF is the exposure frequency (days/year), SA is the skin surface area available for contact (cm^2), BW is the body weight (kg) and AT is the averaging time (days). For non-carcinogenic endpoints, AT = ED x 365 days/year.

For the current assessment, scenarios were based on the once daily use of SLPs. It should be noted that for a once daily exposure frequency, the parameters EV, ED, EF and AT in the equation above cancel out so that exposure becomes a function of dermal permeability (K_p), chemical concentration (C_w), event duration (t_{event}), SA and BW:

$$\mathrm{DA}_{\mathrm{event}} = K_{\mathrm{p}} \times C_{\mathrm{w}} \times t_{\mathrm{event}}$$

The K_p values of ^{14}C-HQ solution have been estimated to be 2.6×10^{-9} cm/s for human skin and 6.3×10^{-9} cm/s for rat skin. However, the dermal absorption of HQ is influenced by other ingredients in the formulation – for example, alcohols increase the dermal absorption of HQ from cosmetics. Therefore, K_p values of commercially available HQ-containing cosmetics should be used in the exposure assessment. Matsumoto *et al.* (2016) examined rat skin permeation rates for four commercially available HQ-containing cosmetic products (0.3% to 3.3% HQ) using a side-by-side diffusion cell system to predict plasma HQ concentrations in humans after dermal absorption and obtained permeation coefficients ranging from 1.2×10^{-9} to 3.1×10^{-7} cm/s, with the highest value being greater than that for the HQ aqueous solution (1.6×10^{-7} cm/s). The highest value for K_p was used for the current assessment.

The values of the parameters used in the current assessment are provided in Table 6.

Table 6. Parameters used in the exposure assessment of hydroquinone in cosmetics

Parameter	Value	Comment
K_p – dermal permeability coefficient of hydroquinone	3.1×10^{-7} cm/s or 0.0011 cm/hour	
C_w – concentration of hydroquinone in cosmetic product	Cream: 9% or 90,000 ppm = 90,000 mg/L or 90 mg/cm^3 Lotion: 10.5% or 105,000 ppm = 105 mg/cm^3	It was assumed that the density of the cosmetic product is 1
T_{event} – event duration	8 hours/event	Since creams and lotions are leave-on cosmetic products, it was assumed that they remain on the skin for 8 hours
DA_{event} – dermal absorption per event	Cream: 0.0011 cm/hour × 90 mg/cm^3 × 8 hours/event = 0.80 mg/cm^2/event Lotion: 0.0011 cm/hour x 105 mg/cm^3 x 8 hours/event = 0.93 mg/cm^2/ event	
SA – skin surface area	Cream: 565 cm^2 Lotion: 15,670 cm^2	The surface area of half the head (face cream) and the mean body surface area (body lotion) of a female, taken from SCCS (2021)
BW – body weight	72 kg	The mean body weight for a New Zealand female (16–64 years), taken from (Cressey, 2016)

Using the earlier equation, the following DAD values were obtained:

$$\text{DAD (cream)} = \frac{0.80\,\frac{\text{mg}}{\text{cm2}} \times 565\ \text{cm2}}{72\ \text{kg}} = \mathbf{6.3\ mg/kg\ bw/day}$$

$$\text{DAD (lotion)} = \frac{0.93\,\frac{\text{mg}}{\text{cm2}} \times 15{,}670\ \text{cm2}}{72\ \text{kg}} = \mathbf{202\ mg/kg\ bw/day}$$

5. RISK CHARACTERISATION

While there are some reports of HQ-containing SLPs causing local (concentration-related) adverse effects, systemic effects on the haematological system and CNS are considered to be the most sensitive endpoints associated with HQ exposure.

The potential for non-carcinogenic health risks posed by HQ in SLPs were assessed based on the hazard quotient, which is the ratio of the estimated systemic exposure of HQ to the p-RfD. As previously mentioned, the high gastrointestinal absorption of HQ following oral exposure means that the p-RfD can be considered as both the external and systemic reference dose. The hazard quotient was calculated using the following equation:

$$\text{Hazard quotient} = \frac{\text{DAD}}{\text{pRfD}}$$

A hazard quotient ≤1 indicates that there would be no adverse health effects, whereas a hazard quotient >1 indicates possible adverse health effects.

The hazard quotients for creams and lotions containing HQ are presented in Table 7.

Table 7. Hazard quotients for the non-carcinogenic risk of creams and lotions containing hydroquinone

Product	Exposure (mg/kg bw/day)	Rfd (mg/kg bw/day)	Hazard quotient
Cream	6.3	0.04	156
Lotion	202		5,000

bw: body weight, Rfd: reference dose

The hazard quotient for both creams and lotions is greater than 1, indicating that the presence of HQ may be a cause for concern with respect to non- carcinogenic effects. However, it should be noted that the results of this Tier 1 assessment are based on worst-case scenarios. HQ containing products are generally recommended for spot treatments and are to be avoided for application to skin areas without pigmented spots. Therefore, if the application of creams was limited to spot areas, e.g., 1/100 of face area, the hazard quotient will be 1.56, still slightly more than 1. Secondly, the concentrations of HQ used in the risk assessment are also the maximum levels detected in creams and lotions, which may overestimate the risks, as such concentrations are highly unlikely to be consistently present in SLPs. Moreover, the values for the skin permeation rate of HQ used in this risk assessment were derived from studies on rat skin, and the permeation of HQ is expected to be slower in humans than in rats, which may further contribute to the hazard quotient being overestimated. Nevertheless, the results of this study suggest that regulatory decisions to ban HQ-containing SLPs except under clinical supervision is well founded.

Local effects are also associated with the use of formulations containing HQ. Formulations containing HQ concentrations >5% have been reported to cause local irritation and leukoderma in humans. Additionally, based on clinical data, the continued use of formulations containing >1% HQ can cause melanin destruction and exogenous ochronosis. Hence, the long-term use of SLPs containing HQ at concentrations up to 10.5% also increases the risk of dermal irritation, leukoderma and exogenous ochronosis.

6. CONCLUSIONS

SLPs are used to lighten skin tone, fade freckles and remove age spots. They are available in the form of creams, lotions, soaps and powders. HQ is used as an active ingredient in some cosmetic SLPs. In New Zealand, cosmetic products are regulated by the NZ EPA through the Cosmetic Products Group Standard 2020 under the HSNO Act, and under this group standard, cosmetic products must not contain HQ. However, HQ can be used by professionals only in artificial nail systems with a maximum concentration of 0.02% (200 ppm) after mixing for use.

Contact dermatitis and exogenous ochronosis are the most common complications in humans from the use HQ containing cosmetic products. Effects on the kidneys, thyroid gland, haemopoietic system and CNS have also been reported in animal studies.

Creams and lotions are the most common types of cosmetic products containing HQ that have been recalled from the market in Europe. Dermal exposure is the most important exposure route for creams and lotions, with oral and inhalation exposure expected to be negligible.

Based on a Tier 1 assessment that considered realistic exposure scenarios for HQ-containing SLPs and the maximum concentrations of HQ reported for creams and lotions, hazard quotients greater than 1 were estimated, indicating that the presence of HQ in creams and lotions may be a cause for concern with respect to non- carcinogenic effects. This conclusion is consistent with the NZ EPA's current regulatory position, which does not permit HQ is cosmetic products. These findings also suggest that surveillance for the presence of HQ-containing SLPs in the New Zealand market may be warranted.

Given the conservative nature of the assumptions adopted in the current risk assessment, further assessment of risks associated with HQ use may be warranted, particularly if New Zealand-specific information were to become available.

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