HEALTH RISK ASSESSMENT:
MERCURY IN SKIN-LIGHTENING PRODUCTS

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by

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HEALTH RISK ASSESSMENT: MERCURY IN SKIN-LIGHTENING PRODUCTS

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**GLOSSARY**

<table>
<thead>
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<th>Term</th>
<th>Definition</th>
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</table>
| Acute toxicity | 1. *Adverse effects* of finite duration occurring within a short time (up to 14 d) after administration of a single *dose* (or *exposure* to a given *concentration*) of a test substance or after multiple doses (exposures), usually within 24 h of a starting point (which may be exposure to the *toxicant*, or loss of reserve capacity, or developmental change, etc.)  
2. Ability of a substance to cause *adverse effects* within a short time of dosing or *exposure* |
<p>| Adverse effect | A change in biochemistry, physiology, growth, development morphology, behaviour, or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to other environmental influences |
| Autoimmune | Of or relating to an immune response by the body against one of its own tissues, cells, or molecules |
| Dermal | Cutaneous, pertaining to the skin |
| Dose | Total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue |
| Dose response | Association between dose and the incidence of a defined biological effect in an exposed population |
| Dose response assessment | Analysis of the relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the changes developed in that organism, system, or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose–response assessment is the second of four steps in risk assessment |
| Epithelium | Sheet of one or more layers of cells covering the internal and external surfaces of the body and hollow organs |
| Erythema | Redness of the skin due to congestion of the capillaries |
| Exposure assessment | Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment |
| Glomerular basement membrane | The basal lamina layer of the glomerulus |
| Glomerulus | A network (tuft) of capillaries in the kidneys that performs the first step of filtering blood |
| Harm | An adverse effect. Damage or adverse effect to a population, species, individual organism, organ, tissue, or cell |</p>
<table>
<thead>
<tr>
<th>Hazard identification</th>
<th>The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpigmentation</td>
<td>Darkening of an area of skin or nails caused by increased melanin</td>
</tr>
<tr>
<td>Incidence</td>
<td>Number of occurrences of illness commencing, injury, or of persons falling ill, during a given period in a specific population usually expressed as a rate</td>
</tr>
<tr>
<td>Injury</td>
<td>Any physical harm or damage serious enough to warrant medical treatment by a health professional either at the scene or in a hospital or primary care practice</td>
</tr>
<tr>
<td>Intentional tremor</td>
<td>A rhythmic purposeless shaking of the muscles that begins with purposeful (voluntary) movement. This tremor does not affect muscles that are resting</td>
</tr>
<tr>
<td>Irritant</td>
<td>Producing inflammation or irritation</td>
</tr>
<tr>
<td>Melasma</td>
<td>A condition characterised by dark, irregular well-demarcated hyperpigmented macules to patches commonly found on the upper cheek, nose, lips, upper lip, and forehead</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Muscular pain or tenderness</td>
</tr>
<tr>
<td>Neurasthenia</td>
<td>A complex of symptoms characterised by chronic fatigue and weakness, loss of memory, and generalised aches and pains</td>
</tr>
<tr>
<td>No observed adverse effects level (NOAEL)</td>
<td>Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure</td>
</tr>
<tr>
<td>Oedema</td>
<td>Abnormal accumulation of fluid in the interstitium, which are locations beneath the skin or in one or more cavities of the body, presenting as swelling</td>
</tr>
<tr>
<td>Oral</td>
<td>Pertaining to or via the mouth</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>Abnormal sensation, e.g. burning, tingling, pricking</td>
</tr>
<tr>
<td>Permanent harm</td>
<td>An adverse effect from which the subject does not recover</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>The presence of an excess of serum proteins in the urine</td>
</tr>
<tr>
<td>Quartan malarial nephropathy</td>
<td>Kidney disease associated with <em>Plasmodium malariae</em> infection</td>
</tr>
<tr>
<td>Risk characterisation</td>
<td>The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. Risk characterisation is the fourth step in the risk assessment</td>
</tr>
<tr>
<td>Segmental sclerosis</td>
<td>Scarring of a portion, but not the whole of kidney glomerulus</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Toxicological endpoints</td>
<td>An observable or measurable biological event or chemical concentration (e.g. metabolite concentration in a target tissue) used as an index of an effect of a chemical exposure</td>
</tr>
</tbody>
</table>
SUMMARY

Skin-lightening products may contain mercury, in the form of inorganic mercury salts, at concentrations up to approximately 20% w/w. Such products are illegal in many countries. In New Zealand, cosmetic products are regulated under the Cosmetic Products Group Standard 2006 under the Hazardous Substances New Organisms Act 1996. Under the group standard, cosmetic products must not contain mercury and its compounds, except for use as a preservative in eye make-up and eye make-up remover. It is unknown how common use of mercury-containing skin-lightening products is in New Zealand, but no cases of intoxication have come to the attention of New Zealand surveillance systems. However, it should be noted that the symptoms of mercury poisoning are often negligible or non-specific and may remain undiagnosed.

A number of overseas case and case series reports of toxicity due to mercury-containing skin-lightening products have been published. Adverse health effects have included non-specific potentially neurological symptoms, clinical renal dysfunction or, less commonly, dermal symptoms. Inorganic mercury compounds have low lipid solubility and are unlikely to cross the blood-brain barrier. It is uncertain how mercury from skin-lightening products contributes to the potentially neurological symptoms reported in some studies. Renal toxicity appears to occur through an immune-mediated mechanism and it is likely that the population will vary in susceptibility to these toxic effects.

Exposure modelling suggests that mercury-containing skin-lightening products represent a public health risk even at the lowest mercury concentrations reported for these products. While assigning plausible different values to model parameters produces a wide range of exposure estimates, to ensure a hazard quotient of less than one across all model variants would require the mercury content of skin-lightening products to be not more than 0.008 mg/kg.

The scientific literature also indicates that use of mercury-containing skin-lightening products may result in mercury poisoning in non-using members of the same household, although the route of exposure is uncertain.
1. INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for cosmetic skin-lightening products containing mercury as an active ingredient. This report will only consider domestic, non-occupational, routine and incidental exposure to mercury-containing skin-lightening products. Exposure scenarios will be developed for the most common or likely exposure events.

1.1 Consumer Products Description – Mercury-containing Skin-lightening Products

Skin-lightening products may be in the form of creams, milks, oils, ointments or soaps (Cristaudo et al 2013; WHO 2011). The terms ‘skin-lightening’, ‘skin-bleaching’ and ‘skin-whitening’ have all been used synonymously to describe such products. These products may contain a range of active ingredients, including mercury, hydroquinone, topical corticosteroids (TCs), hydrogen peroxide, kojic acid, arbutin, nicotinamide, tretinoin, azelaic acid, salicylic acid, phenols and solvents (Cristaudo et al 2013; Desmedt et al 2014). The current report only deals with products containing mercury as the active ingredient.

1.1.1 Mode of action

Mercury inhibits production of the skin pigment melanin in epidermal melanocytes by inactivating sulfhydryl mercaptan enzymes, leading to inactivation of tyrosinase, an important catalyst in melanin production (Engler 2005; Hamann et al 2014). Mercury may be present in skin-lightening products as ammoniated mercury, mercury iodide, mercurous chloride, mercurous oxide, or mercuric chloride (Park and Zheng 2012).

1.1.2 Prevalence of use

Skin-lightening products have a legitimate dermatologic role in the treatment of hyperpigmentation disorders, such as melasma and post-inflammatory hyperpigmentation (Engler 2005; Hamann et al 2014; Ladizzinesski et al 2011). However, such products are also commonly used in a number of African, Asian and Latin American countries and amongst dark-skinned populations in North America and Europe to produce a general cosmetic lightening of the skin (de Souza 2008; Park and Zheng 2012; WHO 2011). Products are mainly applied to the face and hands, but also often to the whole body (Park and Zheng 2012).

Africa

It has been reported that skin-lightening products are used regularly by women in Senegal (27%), Mali (25%), Togo (59%), South Africa (35%) and Nigeria (77%) (UNEP 2008).

A cohort of women in the third trimester of pregnancy \( n = 99 \) was recruited during prenatal visits to a maternity unit in Dakar, Senegal (Mahé et al 2007). Sixty-eight (69%) of the women reported using skin-lightening products for cosmetic purposes during their current pregnancy. Products were applied to the whole body in 58 cases (59%), at least once a day for an average of five years (range three months to 24
years). Use levels were in the range 12-170 g/month. It should be noted that the majority of products used were corticosteroid-based.

A survey amongst randomly-selected market traders in Lagos, Nigeria \((n = 450)\) found that 77% of respondents reported using skin-lightening products (Adebajo 2002). Use of these products was at a similar rate amongst women and men. Hydroquinone-based products were most frequently used, followed by corticosteroid and mercury-based products. Approximately 70% of respondents had used skin-lightening products for 6 months to 3 years, but about 13% had used these products for more than five years. Treatment of skin blemishes and a desire to be more attractive were the most common reasons for using skin-lightening products. Approximately half of those who used skin-lightening products developed side effects, with most of the reported side effects being effects on the skin.

**Middle East**

A survey in Jordan of women arriving at selected pharmacies \((n = 318)\) found that 61% reported using skin-lightening products (Hamed et al 2010). The respondents completed a questionnaire concerning perceptions of skin tone, with strong agreement that lighter skin tones are more beautiful, are perceived to be more beautiful, and improve a woman’s marriage prospects.

A survey in Saudi Arabia of women attending outpatient clinics at a university hospital \((n = 509)\) found that 39% were current users of skin-lightening products (AlGhamdi 2010). Most users of these products \((152/197; 77\%)\) reported using more than 100 g of skin-lightening products per month, with some using up to 600 g per month. Duration of usage varied from 1 to 150 months. Approximately 7% of respondents reported that the product was applied to their whole body. The face was the body area to which products were most commonly applied.

**Asia**

In 2004, more than one-third \((38\%)\) of women surveyed in Hong Kong, Korea, Malaysia, the Philippines and Taiwan used skin lightening products (UNEP 2008).

**Europe**

In a study carried out in Italy (Rome), immigrant (non-Italian) women \((n = 82)\) were recruited at an outpatient and diagnostic facility and were asked to complete a questionnaire (Cristaudo et al 2013). Thirty-three \((40\%)\) women were using or had used skin-lightening products, with duration of use ranging from 8 months to 20 years. It should be noted that 14 skin-lightening products were obtained for analysis, with none containing mercury at concentrations above 1 mg/kg.

Women from Armenia \((n = 60)\), Belarus \((n = 59)\) and Georgia \((n = 63)\) were asked a series of questions about cosmetic use and knowledge of mercury (Armenian Women for Health and Health Environment 2011). Skin-lightening products were reported to be used by 28.3, 10.2 and 49.2% of respondents in Armenia, Belarus and Georgia, respectively.
North America

A survey of households in the Mexico border region of Texas found that 104 of 2194 households (4.7%) included at least one person who had used a specific skin-lightening product in the previous year (Weldon et al 2000).

A cross-sectional study of women attending three Women, Infant and Children’s clinics in New Mexico found that 5 of 185 (2.7%) women interviewed were current users of skin-lightening products (Balluz et al 1997). The median duration of use was seven weeks, while the median frequency of use was seven times per week.

1.1.3 Mercury in skin-lightening products

Table 1 summarises the results of various surveys of the mercury content of skin-lightening products.

Table 1: Summary of surveys of mercury in skin-lightening products

<table>
<thead>
<tr>
<th>Survey country</th>
<th>High mercury products/total products (%)</th>
<th>Highest concentration reported (%)</th>
<th>Claimed countries of manufacture</th>
<th>Study reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>5/19 (26)</td>
<td>1.3</td>
<td>China, Thailand, Vietnam</td>
<td>(Murphy et al 2009)</td>
</tr>
<tr>
<td>Ghana</td>
<td>0/50 (0)</td>
<td>No samples contained more than 1 mg/kg mercury</td>
<td></td>
<td>(Amponsah 2010)</td>
</tr>
<tr>
<td>Mexico</td>
<td>6/16 (38)</td>
<td>3.5</td>
<td>Mexico, Germany</td>
<td>(Peregrino et al 2011)</td>
</tr>
<tr>
<td>Philippines</td>
<td>19/25 (76)</td>
<td>5.2</td>
<td>China, Hong Kong, Taiwan, Germany, Japan, Saudi Arabia</td>
<td>(GMA News 2011)</td>
</tr>
<tr>
<td>Philippines</td>
<td>13/14 (93)</td>
<td>6.1</td>
<td>China, Taiwan</td>
<td>(GMA News 2012)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>11/38 (29)</td>
<td>0.6</td>
<td>Lebanon, Thailand, United Kingdom</td>
<td>(Al-Saleh and Al-Doush 1997)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>2/34 (6)</td>
<td>31.4</td>
<td>USA</td>
<td>(Al-Saleh et al 2011)</td>
</tr>
<tr>
<td>South Africa</td>
<td>4/10 (40)</td>
<td>Not stated</td>
<td>South Africa, Taiwan, UK</td>
<td>(Dlova et al 2012)</td>
</tr>
<tr>
<td>Tanzania</td>
<td>Soaps 3/3 (100)</td>
<td>0.7</td>
<td>United Kingdom</td>
<td>(Glahder et al 1999)</td>
</tr>
<tr>
<td></td>
<td>Creams 0/2 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA (Chicago)</td>
<td>6/50 (12)</td>
<td>3.0</td>
<td>Pakistan</td>
<td>(Gabler and Roe 2010)</td>
</tr>
<tr>
<td></td>
<td>Soaps 1/4 (25)</td>
<td>0.003</td>
<td>Not stated</td>
<td>(Adawe and Oberg 2013; Minnesota Department of Health 2011)</td>
</tr>
<tr>
<td></td>
<td>Creams 10/23 (43)</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Various</td>
<td>33/549 (6.0)</td>
<td>4.6</td>
<td>USA, China, Thailand</td>
<td>(Hamann et al 2014)</td>
</tr>
</tbody>
</table>

1 High mercury products were generally considered to be those containing more than 100 mg/kg of mercury (>0.01%)
2 The country of manufacture was only given for the product with the highest reported mercury content
In 2008-2009, a survey was carried out, analysing samples of skin-lightening products from Kenya, Senegal, India, China, Russia, Kyrgyzstan, Brazil and Mexico (Uram et al 2010). Mercury was only detected at concentrations above the limit of detection (0.07 mg/kg) in 2 of 67 (3%) samples. Both products were purchased and produced in Mexico and contained 0.8 mg/kg and 1325 mg/kg (0.1%) of mercury.

A survey of skin-lightening products sampled in Armenia, Belarus and Georgia (n = 57) reported a maximum mercury concentration of 1.7 ppm (mg/kg) (Armenian Women for Health and Health Environment 2011). However, in general the mercury concentrations reported seemed very low and it is uncertain whether the units of measurement have been accurately reported.

The European Union (EU) operates a market surveillance system, the Rapid Alert System for non-food dangerous products (Rapex). The system allows the 31 participating countries (EU countries, Norway, Iceland and Liechtenstein) and the European Commission to exchange information on products posing a risk to health and safety of consumers and on the measures taken by these countries to do away with that risk. For the period 2005-2014, the Rapex system contains 110 entries for skin-lightening products. Most Rapex alerts for skin-lightening products were due to the presence of hydroquinone (n = 65, 59%). However, 20 alerts (18%) were due to the presence of mercury in skin-lightening products. Concentrations ranged from 21.5 mg/kg to 38,800 mg/kg (3.9%). Where the country of origin was known, all mercury-containing products were from Pakistan or China.

1.2 Regulatory Situation in New Zealand

In New Zealand, regulation of cosmetic products is covered by the Cosmetic Products Group Standard 2006 under the Hazardous Substances New Organisms Act 1996. Under the group standard, cosmetic products must not contain mercury and its compounds, except for use as a preservative in eye make-up and eye make-up remover. The permitted mercury compounds are thiomersal and phenylmercuric salts, to a maximum concentration of 0.007% mercury.

It does not appear that any random surveys of skin-lightening products have been carried out in New Zealand.

1.3 Incident Surveillance in New Zealand

In New Zealand, data on hazardous substance exposure incidents is collated in the Hazardous Substances Surveillance System (HSSS) by the Massey University Centre for Public Health Research (CPHR). For the period 2006 to 2011, 5,827 incidents were reported to HSSS. Of these, none were listed using descriptors that could refer to skin-lightening products.

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Information was provided by the New Zealand National Poisons Centre\(^1\) on the 20 substances accounting for most calls to the centre for each year during the period from 2008 to 2012. Skin-lightening products were not in this ‘top 20’ list in any year for which information was available. However, it should be noted that the symptoms of mercury poisoning are often negligible or non-specific and may remain undiagnosed.

No fatalities due to exposure to skin-lightening products were reported in New Zealand in the period 2006 to 2009.

2 HAZARD IDENTIFICATION

While other ingredients may be present in skin-lightening products, the current assessment only concerns effects due to the presence of inorganic mercury in these products.

2.1 Health Effects – Inorganic Mercury

The adverse health effects due to mercury exposure show some variation, depending on the form of mercury and the route of exposure. Mercury present in skin-lightening products appears to always be inorganic mercury, not organic or elemental mercury. Calomel (mercurous chloride) has often been reported as the source of mercury in these products (Balluz et al 1997; Tlacuilo-Parra et al 2001; Villanacci et al 1996a; Villanacci et al 1996b; Weldon et al 2000), although ammoniated mercury, mercury oxide and mercury iodide have also been reported as ingredients (Engler 2005; McKelvey et al 2011). Mercury-containing skin-lightening products do not always list mercury compounds as an ingredient (Dlova et al 2012; McKelvey et al 2011; Peregrino et al 2011). The route of exposure will be principally dermal. It should be noted that a study of households of women using skin-lightening products found elevated urinary mercury concentrations in some non-users in the same household (Copan et al 2012). However, it is uncertain what the exposure route was for non-users and they were all free from symptoms of mercury intoxication.

Adverse effects due to exposure to inorganic mercury in skin-lightening products are most commonly due to the effect on the kidneys, with neurological and skin effects occasionally reported (ATSDR 1999; JECFA 2011).

2.1.1 Renal effects

Mercury intoxication due to skin-lightening products has frequently been reported as resulting in nephrotic syndrome (NS) (ATSDR 1999; Barr et al 1972). NS is a non-specific kidney disorder, characterised by proteinuria (protein in the urine), oedema and decreased serum proteins (albumen and globulins). There is often no impairment of renal function. Histological analysis of renal biopsy samples usually shows evidence of minimal change disease (MCD) (Sin and Tsang 2003; Tang et al 2013), membranous nephropathy (MN) (Chakera et al 2011; Kibukamusoke et al 1974; Li et al 2010; Oliveira et al 1987) or proliferative nephropathy (PN) (Barr et al 1972).

In MCD, no changes to the kidney tissues are apparent by light microscopy, but electron microscopy demonstrates primary lesions of the podocytes (glomerular epithelial cells) (Meyrier 2013; Waldman et al 2007). The disease is differentially characterised by absence of electron-dense deposits, absence of thickening of the glomerular basement membrane, absence of immunofluorescence and absence of segmental sclerosis (Waldman et al 2007).

MN is characterised by a thickening of the glomerular basement membrane, apparent under light microscopy (Arabi 2012). Electron microscopy reveals the presence of immune deposits in the sub-epithelial region, which can be
demonstrated by immunofluorescence microscopy to contain IgG and C3 (complement component 3) (Arabi 2012; Chakera et al 2011). The presence of immune-dense deposits in MN supports the suggestion that the effects seen on the kidneys following chronic mercury exposure may occur by an autoimmune mechanism (Friberg 1991).

As the name suggests, PN is characterised by an increase number of cells in the glomeruli. Only one study reported PN amongst cases with NS due to mercury exposure (Barr et al 1972).

High rates of remission of NS (>70%) have been reported after cessation of use of skin-lightening products (Barr et al 1972; Li et al 2010).

2.1.2 Neurological effects

A range of potentially neurological symptoms have been reported in cases suffering mercury intoxication due to skin-lightening products, including mild tremors, anxiety, depression and paranoid delusions (Dyall-Smith and Scurry 1990), numbness, tingling (paraesthesia), dizziness, forgetfulness and headaches (Copan et al 2012), insomnia, irritability and weakness (Sin and Tsang 2003).

2.1.3 Dermal effects

A range of effects to the skin have been reported following use of mercury-containing skin-lightening products, including rashes (Li et al 2010), skin discolouration (Dyall-Smith and Scurry 1990; WHO 2011) and scarring (WHO 2011).

2.1.4 Hypertension

While not usually associated with mercury toxicity, hypertension (high blood pressure) was observed in three separate child cases of mercury poisoning (Jefferson Fowles, California Department of Public Health, personal communication, October 2014). In all three cases, mercury poisoning was diagnosed following hospitalisation for hypertension. Hypertension resolved following chelation therapy. The cases were from households where skin-lightening products were used, but mothers stated that the products were never used on the children. The route of exposure is uncertain, but the source of mercury was believed to be the skin-lightening products.

2.2 Absorption

Due to the dermal application of skin-lightening products, a key issue is the degree of absorption of inorganic mercury. Major toxicological assessments have pointed to cases of toxicity following dermal application as evidence that inorganic mercury is absorbed, but concluded that there was no information on the extent of dermal absorption (ATSDR 1999; Friberg 1991; Risher 2003).

Inorganic mercury has been reported to be absorbed by both transdermal (transport across the epidermis) and transappendageal (transport via the sweat glands, sebaceous glands and hair follicles) mechanisms (Chan 2011).
In vitro studies, using isolated human abdominal skin in a Franz diffusion cell, were carried out to examine the transdermal kinetics of mercurous chloride (Palmer et al 2000). An initial rapid increase in the mercury content of the skin and the receiving buffer was observed. It was estimated that 0.8% of mercury from a proprietary skin-lightening product was absorbed into or through the skin, while 3.7% was absorbed from an aqueous preparation. It was noted that abdominal skin is less permeable than facial skin.

A study was carried out in which high-mercury (7.8%) and low-mercury (0.00003%) skin-lightening products were applied to skin of albino or pigmented mice at various frequencies (once a week, once a day, twice a day, three times a day) for one month (Al-Saleh et al 2004). Tissue (brain, kidney, liver) mercury concentrations were highest in animals treated with the high-mercury product, albino mice compared to pigmented mice, and with more frequent applications of products. Concentrations were highest in kidney tissue, followed by liver, followed by brain. The finding of increased mercury concentrations in the brains of treated mice suggests that some of the inorganic mercury from the skin-lightening products is able to cross the blood-brain barrier. Inorganic mercury compounds are usually considered to be unlikely to cross the blood-brain barrier, due to their low lipid solubility (ATSDR 1999).

A follow-up study confirmed that kidney, liver and brain mercury contents were elevated in mice treated with the low mercury skin-lightening product for one month, compared to controls (Al-Saleh et al 2005). Treated animals had reduced body weights compared to controls and histopathological changes were also observed in the kidneys of treated animals and, to a lesser extent, in the livers and brains.

An extension to this study demonstrated similar patterns of mercury deposition in mouse ovaries (Al-Saleh et al 2009).

### 2.3 Placental Transfer

Inorganic mercury is transferred across the placental barrier to a much lower extent than elemental mercury, due to the lower lipophilicity of inorganic mercury compounds (ATSDR 1999; Friberg 1991; Risher 2003). However, a case has been reported that suggests that transmission of mercury from maternal use of mercury-containing soap may be sufficient to result in toxic effects in the infant (Lauwerys et al 1987). The mother had used a soap containing 1% mercuric iodide for 15 years, but the soap was never applied to the infant’s skin. The child was found to have elevated blood (1.9 µg/100 ml) and urine (274 µg/g creatinine) mercury levels, as did the mother (9.11 µg/100 ml and 784 µg/g creatinine for blood and urine, respectively). The child also had signs of renal tubular dysfunction, in addition to bilateral cataracts and moderate iron deficiency anaemia. The investigators concluded that the renal impairment was due to mercury transfer from the mother during the foetal period and probably also during a 1-month lactation period following birth.
2.4 Case Reports

While different case reports often given different values for 'normal' or 'acceptable' concentrations of mercury in blood and urine, the Centers for Disease Control and Prevention (CDC) case definition for inorganic mercury poisoning gives laboratory criteria for diagnosis as:

"An elevated urinary or whole blood mercury concentration. A urinary mercury concentration ≥10 μg/L or a total whole blood mercury concentration ≥10 μg/L is an unusual level of exposure for a person with no known occupational exposure to mercury. Fish consumption can elevate total whole blood mercury concentrations." ¹

In some studies urinary concentrations are given in ‘nmol/L’. A concentration of 10 μg/L is equivalent to 50 nmol/L. Other studies give urinary concentrations in terms of ‘nmol/day’ or ‘μg/day’. Using a standard urinary output of 1500 mL/day, 10 μg/L is equivalent to 15 μg/day or 75 nmol/day.

In the following case studies, the ‘normal’ concentrations given by the authors are quoted.

2.4.1 Australia

A 42-year-old woman presented with symptoms of depression, anxiety and paranoid delusions (Dyall-Smith and Scurry 1990). A blue-black skin pigmentation was apparent. Apart from a mild tremor, no neurological abnormalities were apparent. The woman had been using a depigmenting preparation containing 17.5% mercuric ammonium chloride for 18 years. Blood mercury concentration was 221 nmol/L (normal <60 nmol/L). Urinary mercury excretion was in the range 1050-2200 nmol/L for 24-hour excretion (acceptable <60 nmol/L). The observed blue-black pigmentation was determined to be due to mercury deposition.

2.4.2 Germany

Two women who had used mercury-containing skin-lightening products (3-10% mercury) for 20-25 years experienced recurring symptoms of headaches, dyspnoea (difficult or laboured breathing) and abdominal cramps (Luderschmidt and Plewig 1979). The women were found to have slate-grey skin hyperpigmentation. Metallic deposits were identified in facial biopsies. Treatment with D-penicillamine resulted in increased urinary excretion of mercury, but did not result in resolution of the facial discolouration or other symptoms.

A 56-year-old woman was found to have elevated serum and urinary mercury after prolonged use of a cosmetic mercury-containing cream (Bockers et al 1985). The woman also had a greenish-black nail discolouration. Energy-dispersive x-ray analysis identified mercury in the cells of the nail plate. Treatment with 2,3-dimercaptopropane-1-sulphonate was effective and well tolerated.

A four-year-old girl was found to have elevated urinary mercury (41 µg/L, reference <25 µg/L) following accidental use of a mercury-containing skin-lightening product (Benz et al 2011). Chelation therapy with dimercaptop-1-propanesulphonic acid (DMPS) resulted in increased urinary mercury concentrations (up to 1175 µg/L) and neurological deterioration. Magnetic resonance imaging (MRI) revealed hyperintense lesions in the brain. The lesions and other signs and symptoms resolved after four months. This report suggests that chelation therapy may allow inorganic mercury to cross the blood-brain barrier.

2.4.3 Hong Kong

A 34-year-old woman presented with NS due to MN (Soo et al 2003). She had been using a skin-lightening product for five years containing 0.18% mercury. Physical examination only revealed bilateral oedema of the ankles. However, proteinuria was high (4.9 g/day). Blood mercury was 163 nmol/L (33 µg/L, normal <10 µg/L) and 24 hour urinary mercury was 755 nmol/day (151 µg/day, normal stated to be 10 nmol/day or 2 µg/day).

2.4.4 Kenya

Patients with established NS (n = 60) presenting during a two-year period were questioned and underwent biochemical and histological tests (Barr et al 1972). Thirty-two (53%) of the patients were using or had used skin-lightening products, with duration of use in the range 1-36 months. For those currently using skin-lightening products, urinary mercury concentrations were in the range 90-250 µg/L. Urinary protein in all NS cases was in the range 1.5-20 g/L, while serum proteins were decreased compared to healthy controls. Histology of renal biopsy samples (n = 34) showed MCD lesions (50%), PN (38%) and MN (12%). However, while 82% of cases with MCD lesions had a history of skin-lightening product use, only 24% of cases with other disease types had used these products.

A study in the Kisumu region measured hair mercury and reported symptoms of women using soaps containing up to 1.7% mercury iodide (Harada et al 2001). There was no correlation between hair mercury and duration of soap use. Symptoms included potentially neurological (tremor, lassitude, headache, skin pain, neurasthenia, palpitations, profuse sweating and vertigo) and dermal (black and white blot, dermatitis and oedema) effects.

2.4.5 Mexico

A 30-year-old woman presented with malar rash (a form of facial rash), burning pain on the face exacerbated by sunlight and excessive perspiration (Tlacuilo-Parra et al 2001). In the following two years she also presented with episodes of sudden flushing, erythema of the palms and soles, intentional tremor, sialorrhea (hyper-salivation), pruritis (itchiness), emotional lability, weakness and insomnia. It was discovered that the patient had been using a mercury-containing skin-lightening product (mercury content 22.1%) for about five years. Urinary mercury content was 150 µg/L (normal <20) and blood mercury content was 30 µg/L (normal <14.9).
Symptoms resolved slowly after cessation of use of the product and application of chelation therapy with D-penicillamine.

2.4.6 Senegal

Analysis of scalp hair from 20 Senegalese women, who were using mercury-containing skin-lightening products, found an average hair mercury concentration of 156 mg/kg (Gras and Mondain 1981). The normal mercury content of scalp hair was reported to be <10 mg/kg.

2.4.7 South Africa

A 48-year-old Bantu woman presented with NS (oedema, proteinuria of 7 g/day and serum albumin 0.8 g/100 ml) (Seedat et al 1973). Upon questioning, the woman admitted she had been using a skin-lightening product containing 7.1% ammoniated mercury for eight years. Renal biopsy was suggestive of the late stages of PN. Urinary mercury was determined three weeks after cessation of use of the skin-lightening product, with mercury concentration just above the ‘normal’ range (97.5 μg/L, normal 0-80 μg/L). It should be noted that this ‘normal’ range has a much higher upper limit than other definitions.

Nine black women presented to the neurological department of a hospital with ‘bizarre involuntary movements’ (Saffer et al 1976). All patients had been using skin-lightening products for months or years and had urinary mercury levels in the range 231-2405 μg/L (normal <5).

2.4.8 Taiwan

Four cases of MCD, a disease causing NS, were described in women who had used skin-lightening products (0.7-3.0% mercury) for 2-6 months (Tang et al 2013). All cases had heavy proteinuria (8.2-20.7 g/day, normal <30 mg/day), elevated blood mercury (26-129 nmol/L, reference range <45 nmol/L, equivalent to 5.2-25.8 μg/L, reference range <9 μg/L) and/or elevated urinary mercury (316-2521 nmol/day, reference range <35 nmol/day, equivalent to 63-504 μg/day or 42-336 μg/L, reference range <7 μg/day or <5 μg/L). Use of cosmetic cream was stopped and cases were given chelation therapy with D-penicillamine. Blood mercury levels were normal within 1-7 months, while normal urinary mercury was achieved after 9-16 months. Complete remission of proteinuria occurred in all cases within 1-9 months.

2.4.9 Uganda

A 21-year-old African woman was referred with facial and peripheral oedema, proteinuria (>10 g/day) and decreased serum albumin (Kibukamusoke et al 1974). The case had used a cream containing 10-15% of a mercury compound on her face, neck and hands daily for 1-2 years. MN was diagnosed on the basis of histological examination of renal biopsy samples. Following cessation of use of the skin-lightening product, NS remitted after 6-9 months.
2.4.10 United Kingdom

A 44-year-old woman referred with NS presented with peripheral oedema and proteinuria of 32 g/L (Chakera et al 2011). Renal biopsy showed MN. Following findings of serum mercury of 150 nmol/L (30 μg/L, normal <30 nmol/L or 6 μg/L) and urinary mercury of 16.5 nmol/mmol creatinine (29 μg/g creatinine, normal 5.5 nmol/mmol creatinine or 10 μg/g creatinine), the woman admitted to using a skin-lightening cream on her face. The cream was found to contain 2% mercury. Following cessation of use of the cream, blood and urinary mercury and proteinuria improved, but renal function remained impaired.

A 26-year-old woman was referred with proteinuria of >9 g/day and normal renal function (Chakera et al 2011). Renal biopsy showed MN. Blood mercury was 233 nmol/L and urinary mercury was 77.5 nmol/mmol creatinine. After cessation of use of a skin-lightening cream, NS resolved, although proteinuria remained elevated.

A 46-year-old woman presented with a diagnosis of NS, including peripheral oedema and proteinuria (2.2 g/day) (Oliveira et al 1987). Light and electron microscopy of renal biopsy samples determined changes consistent with a diagnosis of MN. The woman was using a skin-lightening cream that was found to contain 1% mercury. Urinary mercury was 33 nmol/mmol creatinine (normal <5).

2.4.11 United States

During 1995-1996, three cases of mercury poisoning were investigated by state Departments of Health in the southern US ((Villanacci et al 1996b). Case one was a previously healthy 15-year-old boy who presented with symptoms of fatigue, weakness, insomnia, myalgia of his extremities, severe headache, sore throat, cough, constipation, and paraesthesia of his feet and hands. Urinary mercury was found to be 178 μg/L (normal <20) and chelation therapy was initiated. Investigations revealed the case had been using a cream containing 6% mercury daily for five months for treatment of acne. Case two was a 35-year-old woman with urinary mercury concentration of 355 μg/g creatinine (normal <25). The patient had symptoms of paraesthesia (left forearm, right leg, and ear), irritability, and insomnia. The woman had been using a mercury-containing skin-lightening product for 10 years. Case three was a 33-year-old woman with symptoms of weekly severe migraine headaches of 3–4 days’ duration, irritability, fatigue, short-term memory loss, night blindness, and inability to eat products from tin cans because of overt metal taste. The patient’s urinary mercury concentration was 143 μg/g creatinine. She had used a mercury-containing skin-lightening product daily on her face, hands, and chest for approximately six years. All cases were advised to discontinue use of the product, but no follow-up was reported.

A pregnant woman was found to have a blood mercury concentration of 15.2 μg/L (threshold 5.8 μg/L) (Dickenson et al 2013). A follow-up investigation of the woman’s home found elevated mercury vapour concentrations in proximity to two containers of face cream. The creams contained 2.1 and 3.0% of mercury. The face creams were removed. However, the woman was lost to follow-up and it was not possible to assess the impact of this intervention on her mercury status.
2.5  Epidemiological Studies

2.5.1  China

A series of cases (n = 11) with MN due to mercury exposure was examined (Li et al 2010). Four of the cases had a history of using a mercury-containing skin-lightening product. The product was reported to contain 0.8% mercury. Duration of exposure was in the range 4-12 months, with urinary mercury in the range 12-120 µg/L. There was no apparent relationship between duration of use and urinary mercury. Proteinuria was in the range 1.5-3.8 g/day, but decreased to 0.12-0.36 g/day after abstaining from use of skin-lightening products for 12-24 months.

2.5.2  Germany

Elevated blood and urinary mercury concentrations were found in 121 residents of refugee camps occupied by people from Balkan countries (Otto et al 1994). The median urinary mercury concentration was 12 µg/L (range 0.15-770 µg/L). The source of the mercury was determined to be skin-lightening products containing 708 to 17,200 mg/kg of mercury (0.07 to 1.7%).

2.5.3  Hong Kong

Users of skin-lightening products (n = 314) were recruited through a media advertising campaign directing respondents to a study hotline (Sin and Tsang 2003). Most respondents (78%) reported no symptoms. Symptoms reported included headache (12%), insomnia (9%), memory loss (5%), irritability (5%), abdominal discomfort (3%), nervousness (2%), joint pain (2%), weakness (2%), nausea (2%) and hand tremors (1%). Urine and/or blood samples were collected from 286 cream users. Urinary mercury exceeded 20 µg/L in 55% of samples and blood mercury exceeded 10 µg/L in 65% of samples. Associated skin-lightening products were found to contain up to 5.7% mercury. Urinary and blood mercury concentrations were higher in those who had used products more recently, had used products for longer, and had used products with higher mercury concentrations. Paradoxically, those who reported no symptoms had higher mean urinary and blood mercury concentrations than those who reported symptoms.

2.5.4  Malawi

A prospective study of cases presenting with NS (n = 34) found a history of skin-lightening product use in three cases (Brown et al 1977). These cases had been using a product containing 10-15% aminomercuric chloride once or twice a day for 4 months to 10 years. Renal biopsy revealed MN in two cases and quartan malarial nephropathy in one case. All cases ceased using the skin-lightening product, but still exhibited proteinuria up to 18 months later.

2.5.5  USA

Following on from investigations of three cases of mercury poisoning associated with a skin-lightening product (Villanacci et al 1996b) and associated media
announcements, 238 people contacted health authorities to report use of the product (Villanacci et al 1996a). Of 119 people who provided urine samples, 104 (87%) had elevated mercury concentrations (>20 μg/L) in the range 22-1170 μg/L. Elevated urinary mercury was also detected in several close household contacts of product users, who did not use the product themselves. Further details of this investigation were published at a later time point (Weldon et al 2000). Although respondent numbers had increased at the later time point, study findings were not markedly different.

A more detailed analysis and follow-up was reported for Arizona respondents to the media announcements (McRill et al 2000). Of the women users who submitted urine samples (n = 71), 57 (80%) had elevated mercury concentrations (range 22-770 μg/L). Of samples received from non-using family members (n = 18), 9 (50%) contained elevated mercury concentrations (range 29-340 μg/L). Product users reported using the product for periods of three months to 16 years, with most using the product on a daily basis. A range of non-specific symptoms were reported, with the most common symptoms being headaches, weakness, dizziness, depression and anxiety. Only mild proteinuria was seen in four cases (trace to 0.3 g/L). Urinary mercury concentrations decreased at follow-up, from a mean of 170 μg/L at initial screening to a mean of 90 μg/L after an average of 35 days and a mean of 32 μg/L after an average of 104 days.

Co-ordinators of a health study in California identified a Mexican-American family with elevated blood mercury concentrations (Copan et al 2012). Staff from the California Department of Public Health (CDPH) interviewed five household members and identified skin-lightening products containing 2.0-5.7% mercury as the likely source of mercury exposure. The investigation was extended to include family and friends of the family in California and Virginia. In total, 22 people in five households were included in the investigation. Ten people reported use of skin-lightening products, with frequency of use ranging from intermittent to daily and duration of use ranging from months to five years. Six of the users reported non-specific symptoms, including numbness, tingling, dizziness, forgetfulness, headaches, and depression. Non-users were all asymptomatic. Elevated urinary mercury was confirmed in 9 of 10 users (26-317 μg/g creatinine, normal <5) and 6 of 12 non-users (20-276 μg/g creatinine). Mercury vapour concentrations above background were found near cleaning supplies, clothing, and furniture where creams were stored, and near items frequently touched by cream users (range: 17–50 μg/m³). Four months after cessation of use of skin-lightening products, urinary mercury concentrations were still elevated, but had decreased by an average of 45%.

Mercury concentrations were measured in spot urine samples from 1840 randomly-selected adult New York residents (McKelvey et al 2011). Individuals with urinary mercury ≥20 μg/L were interviewed to determine potential sources of exposure. Thirteen individuals were identified with elevated urinary mercury. Mercury-containing skin-lightening products were identified as the main source of exposure in nine of the 13 individuals. Follow-up analysis of skin-lightening creams from local retail outlets found products containing up to 4.2% mercury.
3 DOSE-RESPONSE INFORMATION

3.1 Oral Health-based Exposure Limits

It has been suggested that the most sensitive adverse effect for inorganic mercury and the most appropriate endpoint for mercury risk assessment is formation of mercuric mercury-induced autoimmune glomerulonephritis (Friberg 1991; US Environmental Protection Agency 2012). This appears to be a relevant endpoint for dermal exposure to inorganic mercury through use of skin-lightening products.

US Environmental Protection Agency (USEPA) derived an oral reference dose (oral RfD) for this endpoint of 0.0003 mg/kg bw/day (0.3 μg/kg bw/day). This is based on the lowest observed adverse effect level (LOAEL) following subcutaneous administration in Norway Brown rats and was derived in 1995. The US Agency for Toxic Substances and Disease Registry (ATSDR) derived the same value as a minimum risk level (MRL) for chronic oral exposure to methylmercury (ATSDR 1999). In addition, an acute oral MRL of 0.007 mg/kg bw/day and an intermediate duration MRL of 0.002 mg/kg bw/day were derived for inorganic mercury (ATSDR 1999).

More recently, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) derived a Provisional Tolerable Weekly Intake (PTWI) for inorganic mercury of 4 μg/kg bw (JECFA 2011). The PTWI was derived from the BMDL10 (lower 95th percentile confidence limit for a benchmark dose giving a 10% change in response over baseline) for kidney weight changes in male rats. The PTWI is equivalent to a daily exposure of 0.6 μg/kg bw, or about twice the USEPA oral RfD.

It should be noted that the USEPA oral RfD is based on a LOAEL, rather than a no observed adverse effect level (NOAEL), relates to subcutaneous administration and incorporates a 1000-fold uncertainty factor. The JECFA PTWI, based on a defined point on the dose-response curve, incorporates a 100-fold uncertainty factor.

3.2 Conversion to a Dermal Health-based Exposure Limit

General pharmacokinetic models suggest that orally and dermally administered mercury will follow similar pathways following absorption (ATSDR 1999). Both the oral RfD and the PTWI relate to administered doses or oral exposures. The USEPA’s suggested approach to assessment of dermally absorbed doses (DAD) is to compare them to an absorbed RfD or internal dose (US Environmental Protection Agency 2004), calculated as:

\[ RfD_{ABS} = \text{oral RfD} \times ABS_{GI} \]

Where RfD_{ABS} is the absorbed RfD and ABS_{GI} is the proportion of the administered dose absorbed from the gastrointestinal tract (oral absorption).

USEPA suggest using an oral absorption of 7% when deriving criteria or health advisories for inorganic mercury (US Environmental Protection Agency 2012). This is consistent with the findings of mercury tracer studies in human volunteers that reported 5-10% absorption of inorganic mercury (Rahola et al 1973).
Application of this oral absorption proportion would result in an RfD_{ABS} of 0.021 \mu g/kg bw/day (21 ng/kg bw/day) and a PTWI_{ABS} of 0.28 \mu g/kg bw. The daily equivalent of the PTWI_{ABS} would be 0.04 \mu g/kg bw/day (40 ng/kg bw/day).
4 EXPOSURE ASSESSMENT

While it is plausible that mercury-containing skin-lightening products may be accidentally ingested, there are no reports of this happening. Given that lethal doses of mercuric chloride have been estimated to be in the range 10-42 mg/kg bw (ATSDR 1999; JECFA 2011) and the very high concentrations of mercury in some skin-lightening products, accidental ingestion would be potentially fatal under most scenarios. For example, a 20 kg child accidentally ingesting a skin-lightening product containing 5% mercury would achieve a potential lethal dose after ingestion of 4 g of product.

The following analysis will deal exclusively with intentional dermal exposure by adult women.

It is apparent from analyses of non-users in households where mercury-containing skin-lightening products are being used that other routes of exposure occur (Copan et al 2012). However, such routes of exposure have not been determined and, consequently, cannot be evaluated.

4.1 Dermal Exposure Models

There are two potential approaches to estimating the DAD for mercury from skin-lightening products:

- Estimate the proportion of the applied dose that will be absorbed, or
- Estimate the rate of absorption of the applied dose and the period for which it will be applied.

The first approach has been used in assessment of exposure to consumer products (European Chemical Bureau 2007; European Chemicals Bureau 2003; HERA 2002; 2003; 2009) and has been used in other assessment of hazardous substances in the current series. In this approach dermal exposure is independent of contact time. In the current report, this approach will be referred to as the Consumer Products Method.

The equations for this approach are:

\[
A_{d_{\text{erm}}} = C_{d_{\text{erm}}} \times T_{d_{\text{erm}}} \times \text{Area}_{d_{\text{erm}}} \times \text{BIO}_{d_{\text{erm}}} \times N_{\text{events}} \tag{1}
\]

\[
U_{d_{\text{erm \_pot}}} = \frac{A_{d_{\text{erm}}} \times F_{\text{absorp}}}{BW} \tag{2}
\]

Where:

- External exposure to skin (mg/event) \(A_{d_{\text{erm}}}\)
- Concentration in the product (mg/cm\(^3\)) \(C_{d_{\text{erm}}}\)
- Thickness of the film layer on skin (default = 0.01cm) \(T_{d_{\text{erm}}}\)
- Surface area of skin exposed (cm\(^2\)) \(\text{AREA}_{d_{\text{erm}}}\)
- Bioavailability for dermal exposure (default = 1) \(\text{BIO}_{d_{\text{erm}}}\)
- Number of events per period (usually, events/day) \(N_{\text{events}}\)
Potential dermal uptake rate (mg/kg body weight/day) \( U_{\text{derm pot}} \)

Factor to quantify absorption \( F_{\text{absorp}} \)

Average body weight (kg) \( BW \)

The second approach is that used by USEPA to determine dermal exposure to chemicals in water and assumes that the concentration of the chemical contacting the skin will be constant (US Environmental Protection Agency 2004). In the case of skin-lightening products, the concentration of mercury contacting the skin will decrease as mercury is absorbed, but the rate of absorption is likely to be sufficiently low that the concentration of mercury contacting the skin can be considered to be constant. This approach has been used to assess risks from skin-lightening product use in Cambodia (Murphy et al. 2009). In this approach dermal exposure is dependent on contact time. In the current report, this approach will be referred to as the USEPA Method.

The equations for this approach are:

\[
D\text{AD} = \frac{D_{\text{A}_{\text{event}}} \times E\text{V} \times E\text{D} \times E\text{F} \times S\text{A}}{B\text{W} \times A\text{T}} \quad (3)
\]

\[
D_{\text{A}_{\text{event}}} = K_p \times C_w \times t_{\text{event}} \quad (4)
\]

Where:

- Dermally absorbed dose (mg/kg bw/day) \( D\text{AD} \)
- Absorbed dose per event (mg/cm\(^2\) – event) \( D_{\text{A}_{\text{event}}} \)
- Event frequency (events/day) \( E\text{V} \)
- Exposure duration (years) \( E\text{D} \)
- Exposure frequency (days/year) \( E\text{F} \)
- Skin surface area available for contact (cm\(^2\)) \( S\text{A} \)
- Body weight (kg) \( B\text{W} \)
- Averaging time (days) \( A\text{T} \)
- Dermal permeability coefficient of compound in water (cm/hour) \( K_p \)
- Chemical concentration in water (mg/cm\(^3\)) \( C_w \)
- Event duration (hours/event) \( t_{\text{event}} \)

For non-carcinogenic endpoints, \( A\text{T} = E\text{D} \times 365 \text{ days/year} \)

For soluble inorganic mercury salts, \( K_p = 0.001 \text{ cm/hour} \)

4.2 Parameters for Exposure Scenarios for Mercury-containing Skin-lightening Products

Both of the exposure assessment methods outlined above were used to determine exposure to mercury from the use of skin-lightening products.
4.2.1 Concentration of mercury in skin-lightening products

It is unknown what concentrations of mercury may be present in skin-lightening products available in New Zealand. For the current exercise, concentrations of 1 and 5% (10,000 and 50,000 mg/kg) were assessed.

4.2.2 Frequency of use of skin-lightening products

A study in the Mexico border region of the US found median usage frequency for skin-lightening products of seven times per week (once daily) (Balluz et al 1997). Another study in the same region reported that most users of skin-lightening products reported using them once daily (McRill et al 2000). Similarly, a number of the case reports in the literature report once daily use of skin-lightening products (Kibukamusoke et al 1974; Oliveira et al 1987; Soo et al 2003; Tlacuilo-Parra et al 2001; Weldon et al 2000). Some studies reported the frequency of use as at least once daily (AlGhamdi 2010; Mahé et al 2007; Petit et al 2006).

For the current study, scenarios were based on once daily use of skin-lightening products. It should be noted that for once daily exposure frequency, the terms EV, ED, EF and AT in equation (3) cancel out and exposure becomes a function of dermal permeability ($K_p$), chemical concentration ($C$), event duration (t-event), body surface area (SA) and body weight (BW).

4.2.3 Body weights

Exposure was assessed for New Zealand women, aged 15 years and older. Based on data from the 2009 Adult Nutrition Survey, the weighted mean body weight for women aged 15 years and older is 72.6 kg, while the 5th percentile body weight is 49.9 kg (University of Otago and Ministry of Health 2011).

4.2.4 Surface area exposed

Studies suggest that skin-lightening products are most commonly applied to the face (AlGhamdi 2010; Balluz et al 1997; Chakera et al 2011; Copan et al 2012; Hamed et al 2010; Soo et al 2003; Tlacuilo-Parra et al 2001), although in some studies the majority of respondents reported applying the products to their whole body (Adawe and Oberg 2013; Mahé et al 2007).

Scenarios were developed for use of the products only on the face and for use on the whole body. The EPA Exposure Factors Handbook (2011) gives body surface area values for adult women in the range 1.69-1.89 m$^2$ (16,900-18,900 cm$^2$), with a decade average of 1.82 m$^2$ (US Environmental Protection Agency 2011). The decade average was used for the current study. For adult females (21+ years) the head represents 6.2% of the body surface area. For the current study, it has been assumed that the face will account for approximately half of the head area, an average of 0.056 m$^2$ (560 cm$^2$).

It should be noted that body surface area varies, depending on other physical characteristics. USEPA have determined that formula (5) was able to explain more
than 99% of the variation in measured body surface area (US Environmental Protection Agency 2011).

\[ SA = a_0 \times H^{a_1} \times W^{a_2} \]  

(5)

Where:

- Body surface area (cm\(^2\)) \(SA\)
- Height (cm) \(H\)
- Body weight (kg) \(W\)
- Derived constants \(a_0, a_1, a_2\)

The optimised values for the derived constants are \(a_0 = 0.0239, a_1 = 0.417\) and \(a_2 = 0.517\).

While it is apparent from this formula that a woman at the 5\(^{th}\) percentile of body weight is highly likely to have a lower body surface area than a woman with an average body weight, it is not possible to say how much lower the body surface area will be without knowledge of the associated height. Examination of data from the 2009 Adult Nutrition Survey shows no correlation between female height and weight \((R^2 = 0.08)\) (University of Otago and Ministry of Health 2011).

To gain an estimate of the body surface area for a woman at the 5\(^{th}\) percentile of body weight, body surfaces areas were calculated, using formula (5), for each woman respondent in the 2009 Adult Nutrition Survey and resulting areas were averaged for all respondents with body weights within 0.5 kg of the 5\(^{th}\) percentile weight (49.9 kg). The resultant average body surface area was 1.49 m\(^2\) (range 1.44-1.56 m\(^2\)).

It is worth noting that applying weighted mean heights (162 cm) and weights (72.6 kg) for New Zealand women from the 2009 Adult Nutrition Survey to formula (5) gives a predicted mean body surface area for New Zealand women of 1.82 m\(^2\), the same value as derived from US data. The weighted mean of the individually calculated body surface areas yields the same value.

Using these New Zealand specific estimates of body surface area, it can further be estimated that an average New Zealand adult woman will have a face area of 560 cm\(^2\), while a woman at the 5\(^{th}\) percentile of body weight will have a face area of 460 cm\(^2\).

4.2.5 Duration of exposure per event

It should be noted that this parameter is only required for exposure calculations using the USEPA approach.

It is uncertain, from the literature, whether skin-lightening products fully absorb into the skin or sit on the skin surface, forming a ‘cake’. One reference was found that stated that “these products are supposed to be applied to the skin to dry overnight” (Pan American Health Organization (PAHO) 2012).
In vitro studies of mercury absorption from skin-lightening products suggest that little additional mercury is absorbed after the first 3 hours (Palmer et al 2000).

Exposure estimates were derived for durations of exposure of 1, 3 and 8 hours, the latter to represent an overnight application.

4.2.6 Film thickness

The dermal exposure calculation that has been used for consumer products (equations (1) and (2)) includes a term for thickness of a film adhering to the body \((T_{\text{derm}})\). The default thickness is 0.01 cm. The film thickness multiplied by the surface area exposed give an estimate of the volume of product adhering to the body.

For application of skin-lightening cream to the face of an average woman, a film thickness of 0.01 cm would equate to 5.6 cm\(^3\) per application, while application to the whole body would require 182 cm\(^3\) per application. Assuming the density of these creams would be similar to an oil-water mixture (0.93 g/cm\(^3\)), this would equate to 5.2 or 169 g per application for the face and whole body, respectively.

Two surveys of use patterns for skin-lightening products report relevant data. A study in Dakar, Senegal (West Africa) reported that most users used skin-lightening products at least once a day, with most respondents applying the products to their whole body (Mahé et al 2007). The average amount of product used was 60 g/month (2 g/day). A study in Riyadh, Saudi Arabia reported that most respondents used skin-lightening products at least once a day, with most only applying the product to their face (AlGhamdi 2010). The average amount of product used was 90 g/month (3 g/day).

To provide some context, it has been estimated that a single application of sun screen or body lotion, cream-type products that would be applied to a high percentage of the body surface, would be 3.2-9.2 g, while a single application of facial cleaning lotion or shaving foam/gel would be 1.6-4.0 g (Biesterbos et al 2013; US Environmental Protection Agency 2011). This suggests that applications to the whole body are likely to be applied more sparingly than application to the face.

For the current exercise it was assumed that application of skin-lightening products to the face only will use 3 g (3.2 cm\(^3\)) of product, while application to the whole body will use 6 g (6.5 cm\(^3\)) of product. These volume estimates replace the terms \(T_{\text{derm}}\) and \(\text{AREA}_{\text{derm}}\) in equation (1).

4.2.7 Absorption factor

Little information is available on the dermal absorption of mercury from skin lightening products. An in vitro study found that 0.8% of mercury was absorbed from a proprietary skin-lightening cream, while 3.7% of mercury was absorbed from an aqueous phase, isolated from the proprietary cream by centrifugation (Palmer et al 2000). For the current exercise, these two estimates were used after rounding up to 1 and 4%, respectively.
4.3 Exposure Assessment

Table 2 summarises estimate of exposure to mercury from use of skin-lightening products use the various parameter options outlined in the previous section and employing the two calculation methods (USEPA and Consumer Products).

Table 2: Mercury exposure (mg/kg bw/day) for an adult woman due to use of skin-lightening products

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>5\textsuperscript{th} percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td>72.6</td>
<td>49.9</td>
</tr>
<tr>
<td>SA(body) (cm\textsuperscript{2})</td>
<td>18,200</td>
<td>14,900</td>
</tr>
<tr>
<td>SA(face) (cm\textsuperscript{2})</td>
<td>560</td>
<td>460</td>
</tr>
<tr>
<td></td>
<td>C = 1% Hg</td>
<td>C = 5% Hg</td>
</tr>
<tr>
<td><strong>USEPA Method</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face only, event duration = 1 hour</td>
<td>0.077</td>
<td>0.386</td>
</tr>
<tr>
<td>Face only, event duration = 3 hour</td>
<td>0.231</td>
<td>1.16</td>
</tr>
<tr>
<td>Face only, event duration = 8 hour</td>
<td>0.617</td>
<td>3.09</td>
</tr>
<tr>
<td>Whole body, event duration = 1 hour</td>
<td>2.51</td>
<td>12.5</td>
</tr>
<tr>
<td>Whole body, event duration = 3 hour</td>
<td>7.52</td>
<td>37.6</td>
</tr>
<tr>
<td>Whole body, event duration = 8 hour</td>
<td>20.1</td>
<td>100</td>
</tr>
<tr>
<td><strong>Consumer Products Method</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face only, 1% absorption</td>
<td>0.004</td>
<td>0.022</td>
</tr>
<tr>
<td>Face only, 4% absorption</td>
<td>0.018</td>
<td>0.088</td>
</tr>
<tr>
<td>Whole body, 1% absorption</td>
<td>0.009</td>
<td>0.045</td>
</tr>
<tr>
<td>Whole body, 4% absorption</td>
<td>0.036</td>
<td>0.179</td>
</tr>
</tbody>
</table>

BW = body weight, SA(Face) = surface area of the face, SA(body) = surface area of the body, C = concentration, Hg = mercury

The two methods of estimating the absorbed dose of mercury due to dermal exposure give quite different results. The USEPA method assumes that absorption will be uniform over the exposure period. This may not be realistic for skin-lightening products, as in vitro skin absorption studies with a skin-lightening product suggested
that the majority of mercury absorption occurs soon after initial contact (Palmer et al 2000).

It should be noted that lethal doses of mercuric chloride have been estimated to be in the range 10-42 mg/kg bw (ATSDR 1999; JECFA 2011) and that the upper estimates of exposure by the USEPA calculation method are in excess of this dose range. It would appear that either this model or the model parameters chosen are inappropriate for assessment of this exposure scenario.

The minimum estimated exposure, by either method, is 0.004 mg/kg bw/day (4 μg/kg bw/day).
5 RISK CHARACTERISATION

While there are some reports of skin-lightening products causing local (concentration-related) adverse effects, systemic effects on the kidney are considered to be the most sensitive endpoint associated with mercury exposure (ATSDR 1999; JECFA 2011; US Environmental Protection Agency 2012).

By assuming that 7% of an ingested dose will be absorbed, estimates for an absorbed reference dose can be derived. The absorbed reference dose is 21 ng/kg bw/day, if based on the EPA oral reference dose (US Environmental Protection Agency 2012) or 40 ng/kg bw/day, if based on the JECFA PTWI (JECFA 2011).

Risk relative to these reference doses can be expressed as a dermal hazard quotient ($HQ_{derm}$) where:

$$HQ_{derm} = \frac{DAD \text{ or } U_{derm \, pot}}{RFD_{Abs}}$$  \hspace{1cm} (6)

A hazard quotient greater than one indicates the potential for adverse health effects.

The lowest estimated exposure to mercury due to dermal contact is 4 μg/kg bw/day or 4000 ng/kg bw/day. This equates to a minimum $HQ_{derm}$ of 100-190, depending on which reference dose is used. It is clear from this assessment that dermal application of skin-lightening products containing 1% or more mercury is not a safe practice, no matter what model or model parameters are employed.

Calculations were carried out to determine concentrations of mercury in skin-lightening products that may be considered safe. That is, concentrations that would result in a $HQ_{derm}$ of less than one, when applied to the exposure scenarios summarised in Table 2. The maximum concentration of mercury that would result in a $HQ_{derm}$ less than one for any of the scenarios summarised in Table 2 is approximately 90 mg/kg, for the scenario of an average body weight women applying the product only to her face with a product mercury concentration of 1% and an absorption of 1%, using the Consumer Product method and the JECFA reference dose. However, this mercury concentration would still result in $HQ_{derm}$ values greater than one for most of the scenarios in Table 2. The maximum concentration of mercury that would result in a $HQ_{derm}$ less than one for all scenarios summarised in Table 2 is approximately 0.008 mg/kg.

Toxicity due to use of skin-lightening products has been associated with non-specific potentially neurological symptoms or renal dysfunction. It is unfortunate that studies on the effects of skin-lightening products have either reported potentially neurological symptoms or involved clinical investigation of renal function, but not both. Dermal effects have only rarely been reported (Dyall-Smith and Scurry 1990; Ludersschmidt and Plewig 1979; Tlacuilo-Parra et al 2001). Hypertension has also been reported in children exposed to mercury due to household use of skin-lightening products.

Inorganic mercury compounds, used in skin-lightening products, have low lipid solubility and it is generally considered that they do not cross the blood-brain barrier (Park and Zheng 2012). However, studies in laboratory animals have shown...
increased brain mercury concentrations following dermal application of skin-lightening products (Al-Saleh et al 2004; Al-Saleh et al 2005).

There is considerable evidence that the effects of inorganic mercury on the kidneys are mediated through an immune mechanism (Druet et al 1978; Rowley and Monestier 2005; Schiraldi and Monestier 2009; Schwenk et al 2009). Studies in rodents have demonstrated genetic variability in susceptibility to renal toxicity due to inorganic mercury (Schiraldi and Monestier 2009) and it is likely that this is also true of the disease in humans, with some people being susceptible, while others are resistant. This would help to explain why some long-term users of skin-lightening products remain asymptomatic and may also help to explain why neurological symptoms dominate in some cases while others exhibit mainly kidney involvement.
6 CONCLUSIONS

Skin-lightening products may contain mercury, in the form of inorganic mercury salts, at concentrations up to approximately 20% w/w. In New Zealand, cosmetic products are regulated under the Cosmetic Products Group Standard 2006 under the Hazardous Substances New Organisms Act 1996. Under the group standard, cosmetic products must not contain mercury and its compounds, except for use as a preservative in eye make-up and eye make-up remover. It is unknown how common use of mercury-containing skin-lightening products is in New Zealand, but no cases of intoxication have come to the attention of New Zealand surveillance systems.

A number of overseas case and case series reports of toxicity due to mercury-containing skin-lightening products have been published. Adverse health effects have included non-specific potentially neurological symptoms, clinical renal dysfunction or, less commonly, dermal symptoms. Inorganic mercury compounds have low lipid solubility and are unlikely to cross the blood-brain barrier. It is uncertain how mercury from skin-lightening products contributes to the potentially neurological symptoms reported in some studies. Renal toxicity appears to occur through an immune-mediated mechanism and it is likely that the population will vary in susceptibility to these toxic effects.

Exposure modelling suggests that mercury-containing skin-lightening products represent a public health risks even at the lowest mercury concentrations reported for these products. While assigning plausible different values to model parameters produces a wide range of exposure estimates, to ensure a hazard quotient of less than one across all model variants would require the mercury content of skin-lightening products to be not more than 0.008 mg/kg.
7 REFERENCES


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