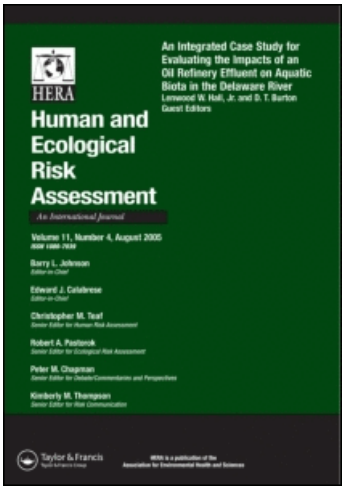

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Mercury Contamination of Skin Whiteners in Cambodia

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ABSTRACT

Eleven of 41 brands of skin whiteners that were collected in Phnom Penh, Cambodia, and processed with a screening kit contained more than 2000 μg/g mercury. Risk analysis indicates that these 11 brands were toxic. Nine of 19 of these skin whiteners analyzed with cold vapor atomic absorption (CVAA) spectrophotometry exceeded Association of Southeast Asian Nations (ASEAN) guidelines for cosmetic good manufacturing practice limit on mercury of 1 μg/g. The most contaminated whitener analyzed by CVAA had 12,590 μg/g mercury. The mercury-containing products were labeled as produced in Thailand, China, Taiwan, Vietnam, the United States, and an unidentified country. Eight other products (antifungal, steroids, and antibiotics) were sold as additives to be mixed into whitener concoctions. In the 19 samples analyzed with CVAA, there was a significant association between the mercury content and a label "for export only." Labeling of sampled products varied from detailed to slight, with none containing Khmer instructions. Variability in mercury content of some products appeared to reflect copying of brand names with very similar packaging.

Key Words: women, export, trade, cosmetics, mercury, skin whitener.

INTRODUCTION

The global concern over mercury toxicity has fueled new legislation by every major government to control the trade in mercury. Recent projections of extensive monitoring predict a doubling of mercury concentrations in the North Pacific

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Ocean from 1995 by 2050 (Sunderland *et al.* 2009). Combustion of fossil fuels is the greatest anthropogenic source of mercury. Important local sources of mercury contamination have often been the pulp and paper, battery, and mining industries (Parsons and Percival 2005). Direct mercury toxicity has also come from a variety of unexpected sources such as cosmetics and folk medicine (Glenn 2008).

One of the first cases of mercury contamination in Cambodia was associated with an illegal shipment from Taiwan of 2700 metric tons of industrial wastes containing a high concentration of inorganic mercury (Hess and Frumkin 2000, p. 331). The authors stated that "at least six deaths and hundreds of injuries have been associated with this incident." Hess and Frumkin stressed the importance of prevention and preparedness in containing emergencies in developing countries.

Cambodia also has a growing number of artisanal miners discharging mercury (Murphy *et al.* 2009). It is difficult for a developing country to stop poor people from using mercury to extract gold. Organizations like the United Nations Development Programme (UNDP) have tried to control the sale of mercury and some progress is being made. The UNDP also has encouraged use of retorts to recycle mercury and if the price of mercury were higher, miners would more readily use retorts (Spiegel *et al.* 2006; Veiga *et al.* 2006).

Agusa *et al.* (2005) examined levels of mercury in hair samples from Cambodia and found high levels from individuals in Phnom Penh and nearby Kean Svay. Phnom Penh is the capital and largest city in Cambodia. Although Kean Svay still has rural elements, the rapid growth of Phnom Penh has spilled into Kean Svay, which is now basically a satellite district of Phnom Penh. Agusa *et al.* (2005) found 10 of 60 hair samples from urban areas had more than 10 μg/g of mercury and three of 60 samples in the urban settings had extreme levels of mercury (190, 70, and 60 μg/g). There was a gender-related trend to higher levels of mercury in Kean Svay but no obvious trend in rural samples. The 34 hair samples from other more remote villages did not contain more than 10 μg/g mercury. Fish analysis by Agusa *et al.* (2005) indicated that fish could not be the source of mercury contamination in Phnom Penh. The mean mercury concentration of 99 ng/g found in 160 fish samples from the Mekong River by Murphy *et al.* (2009) would not require any restriction of fish consumption in Canada (http://www.ene.gov.on.ca/cons/590b12_intro.pdf) and could not produce the extremes of mercury found by Agusa *et al.* in hair samples. Agusa *et al.* also dismissed the mercury wastes from Taiwan as the cause of contamination in Phnom Penh and they were unable to identify the source.

Assessments of mercury associated primarily with gold mining by Murphy *et al.* (2006) differed from those of Agusa *et al.* (2005) in a few ways. Murphy *et al.* (2006) processed 38 hair samples from men in Phnom Penh and found none with more than 10 μg/g mercury. Nine of these men were goldsmiths; no women were goldsmiths. The other 29 men were methylamphetamine addicts; female addicts were not available. In some locations, mercury is used to make this drug but not apparently in Phnom Penh. Second, none of 49 women Murphy sampled in remote villages of northeast Cambodia had >10 μg/g of mercury in their hair. Third, in northeast Cambodia the eight hair samples (of 119) containing >10 μg/g were associated with gold miners working with mercury. The results of Agusa's team and Murphy's team suggest there was a regional and gender-linked source of mercury independent of gold processing. The most commonly reported source of mercury

contamination that is strongly gender-linked and urban is mercury in skin whiteners (Glenn 2008).

Mercury is one of the ingredients in skin whiteners used to block production of melanin. Al-Saleh *et al.* (2004) demonstrated with mice that mercury in a skin whitener was readily absorbed through the skin as evidenced by its accumulation in the brain, kidney, and liver tissues with the kidney having the highest mercury content. Women from many parts of the world often use these whiteners to look like a richer class or to satisfy someone's perception of beauty (Rondilla *et al.* 2007; Glenn 2008). Few men use these products. In one survey in Texas, near the Mexican border, the users were 96% women (Weldon *et al.* 2000). In a clinical review in Hong Kong 99% of respondents using skin creams were women (Sin and Tsang 2003). In another survey in Nigeria 72.4% of users were women (Adebajo 2002). Although there has been no quantification of skin color, it was apparent that women in the remote Cambodian villages were much darker than women in and near Phnom Penh. Potential explanations for the colour difference include a different genetic population in the city, more exposure to sun in the country or skin whiteners that are readily available in Phnom Penh and Kean Svay but not available in the remote villages we sampled.

The purpose of this article was to test the hypothesis that women in Phnom Penh are using skin whiteners contaminated with mercury.

METHODS

In July 2007, 19 skin whiteners were purchased from Boeng Keng Kong and Central (Thmei) markets in Phnom Penh. Samples collected in 2007 were then analyzed in the United States at the University of California, Davis, Department of Environmental Science and Policy. Samples were analyzed for total mercury by standard cold vapor atomic absorption (CVAA) spectrophotometry, using a dedicated Perkin Elmer Flow Injection Mercury System (FIMS) with an AS-90 autosampler, following digestion under pressure at 95°C in a mixture of concentrated nitric and sulfuric acids with potassium permanganate.

Analytical quality assurance/quality control (QA/QC) samples were subjected to the same acid digestion, physical and chemical treatment, and detection as analytical samples and included: blanks, aqueous standards, continuing control standards, standard reference materials with certified levels of mercury, laboratory split samples, matrix spike samples, and matrix spike duplicates. Performance was tracked with control charts. QA/QC results were all within control limits. However, due to the extremely high mercury levels of some of the samples, re-analysis with smaller sample aliquots was necessary to bring those sample results into the linear range of the detection unit.

In June 2008, 17 skin whiteners were collected in the O'Russei market in Phnom Penh. In December 2008, 24 skin whiteners were purchased from Boeng Keng Kong, Central, and Russian (Toul Tom Pong) markets in Phnom Penh. In April 2009, two replicates of whiteners known to have high mercury levels were collected from both Central and Boeng Keng Kong markets. The products of these four markets are representative of the beauty supplies used by most Khmer woman but

not of the more expensive products available in some shops that are not affordable to most Khmer women. The samples collected in 2008 and 2009 were analyzed with a less precise but potentially more widely accessible new mercury screening kit developed by the Department of Medical Science (DMSC) of Thailand and marketed by JSP Pharmaceutical Manufactory (Thailand) Co. Ltd. The ASEAN (Association of Southeast Asian Nations) suggested in January 2008 to use screening kits for skin whiteners containing mercury (ASEAN 2009). The distributor reports that these kits detect mercury above a threshold level of 1500 μg/g. The method involves formation of ammonia that then reacts in the head space of a test tube with litmus paper. There is an obvious gradation in color development of the litmus paper. We used the results of the 19 samples processed by CVAA to segregate samples into three classes: low mercury (brown), >2000 μg/g of mercury but less than 8000 μg/g of mercury (green), and >8000 μg/g of mercury (blue). Note that although the supplier of kits states that the detection limit is 1500 μg/g, they supplied no standards or colour scale for calibration and we chose to use the results of our CVAA analysis for calibration. The supplier currently only provides the method in Thai, but a translation is available from this article's senior author.

First attempts by the senior author to purchase skin whiteners resulted in hesitations, higher prices, and a different communication. In 2007, samples were collected by a young Khmer lady posing as if she was about to use them. In 2008, some vendors said they were afraid to sell our Khmer lady "customer" copied products and would only sell the first-grade products. At these times, we did not purchase the first-grade products but we cannot know if other vendors suspected our intentions and only sold legal products. Limited reviews of similar products in the Mahboonkrong (MBK) shopping center in Bangkok, Thailand, were restricted by vendors not cooperating with the senior author.

RESULTS

Mercury in Samples Collected in 2007

Nine of 19 sampled skin creams collected in Phnom Penh contained mercury exceeding ASEAN Guidelines for Cosmetic Good Manufacturing Practice (2008) of 1 μg/g. The U.S. Food and Drug Administration's (USFDA's) limit on mercury in cosmetics is the same (USFDA 2000). Five of the 19 skin creams contained more than 2000 μg/g of mercury (Table 1). There was a significant trend among the products that were labeled "for export only." A Mann-Whitney U Test of the concentration ranked creams indicated that the creams that were marked "for export only" were significantly ($\alpha = 0.03$) more contaminated with mercury than those without this distinction. The most contaminated cream contained 12,590 μg/g of mercury. That particular cream was labeled from mainland China, but products apparently from Thailand and Vietnam also contained very high levels of mercury.

Mercury in Samples Collected in 2008 and 2009

A mercury screening kit was used to detect levels greater than a threshold of 2000 μg/g in 11 of 41 brands of skin whiteners (Table 2). Agreement between the

Table 1. Skin cream samples from Phnom Penh, 2007, analyzed by CVAA.

Product	Country of origin	Hg μg/g	Market label
C1	China	12,590	For export only
Th1	Thailand	8,578	For export only
V1	Vietnam	3,449	
Th2	Thailand	2,751	For export only
Th3	Thailand	2,292	For export only
Th4	Thailand	84	For export only
V2	Vietnam	67	
Th5	Thailand	26	
Th6	Thailand	19	For export only
Th7	Thailand	0.51	
Th8	Thailand	0.43	For export only
Th9	Thailand	0.17	
Th10	Thailand	0.15	
Th11	Thailand	0.06	
Th12	Thailand	0.04	
V3	Vietnam	0.02	
Th13	Thailand	0.02	
Th14	Thailand	0.01	
C2	China	0.01	

ASEAN guidelines for cosmetic good manufacturing practice limit on mercury in cosmetics is 1 μg/g.
(http://www.bfad.gov.ph/ACCSQ%20COSMETIC/converted%20files/Appendix%20VI_CosmeticGMP.pdf).
U.S. Food and Drug Administration limit on mercury in cosmetics is also 1 μg/g (http://www.cfsan.fda.gov/~dms/cos-210.html).

results of CVAA spectrophotometry and the kit was excellent in all 19 samples that could be compared. Moreover duplication of subsamples was consistent. Eight of the 11 brands contaminated with more than 2000 μg/g mercury were labeled "for export only." Six of these eight contaminated whiteners contained >8000 μg/g Hg. Only 3 of 30 brands without the label "for export only" had detectable mercury with the screening kit. Comparison of the dataset with the label "for export only" and the dataset without this label with a Kolmogorov-Smirnov test indicates that the differences are highly significant ($p = .002$). There was some inconsistency in the presence of mercury in replicated products (Table 3). Ideally statistical analysis would be done with a larger dataset that also measured other illegal additives such as hydroquinone and retinoic acid. However the current analysis does suggest covert production and exporting. International trade in these products should be evaluated using government officers. In December 2008, a small review of skin whiteners in the Mahboonkrong (MBK) shopping center in Bangkok identified four Thai skin whiteners marked "for export only." The Thai government has been enforcing their new regulations for mercury in skin whiteners but the vendors were very uncooperative.

Since the screening kit is only able to detect mercury in samples with more than 1500 μg/g of mercury, we first used the results of CVAA analysis to pick five sets of

Table 2. Skin whiteners from Phnom Penh, 2008, analyzed by screening kit.

Code	Country	Hg-kit	Export*	Price	Bar	Size	Comments
Th1	Thailand	>8000	Y	1500	N	5	For sensitive skin
Th2	Thailand	>2000	Y	1200	N	4	Turmeric cream
Th3	Thailand	>2000	Y	1200	Y	4	Herbal whitening
Th4	Thailand	ND	Y	1200	Y	4	Bio-lab tested
Th5	Thailand	ND	N	1200	Y	5	Kojic acid, Vit. E
Th6	Thailand	ND	Y	1000	Y	4	Bio-Lab tested
Th7	Thailand	ND	Y	1100	Y	4	Vit. E, stearic acid
Th8	Thailand	ND	Y	2000	Y	5	Titanium oxide, Vit. E
Th9	Thailand	ND	N	1000	Y	6	Little English
Th10	Thailand	ND	N	1200	Y	4	Little English
Th11	Thailand	ND	Y	1500	Y	5	Little English
Th12	Thailand	ND	N	1300	Y	3	Pearl cream
Th13	Thailand	ND	N	1200	N	5	Pearl cream
Th14	Thailand	ND	N	1200	Y	4	Nourishing cream
Th15	Thailand	>2000	Y	1200	N	4	Vit. C &E
Th16	Thailand	ND	Y	1000	Y	3	Kojic acid, Vit. E
Th17	Thailand	ND	Y	1200	N	5	Squalene, titanium oxide
Th18	Thailand	>8000	Y	1000	Y	4	Vit. C, fruitamin, glycerin
Th19	Thailand	ND	Y	1000	Y	4	Curcuma extract, Vit. E
Th20	Thailand	ND	Y	6000	Y	11	No lead Hg hydroquinone
Th21	Thailand	ND	Y	1500	Y	3	Pearl extracts
Th22	Thailand	ND	N	1200	N	4	No lead Hg hydroquinone
Th23	Thailand	ND	N	1200	N	4	No English
Th24	Thailand	ND	N	2000	Y	3	Hydrolized pearl
Th25	Thailand	>2000	N	1200	N	3	Acne, melasma cream
V1	Vietnam	>2000	Y	1500	N	3	Titantium oxide, olive oil
V2	Vietnam	ND	N	500	N	3	Pearl cream
V3	Vietnam	ND	Y	600	N	4	Penetrates instantly
V4	Vietnam	ND	N	1600	Y	4	Pimple cream
V5	Vietnam	ND	N	300	N	4	Little English
V6	Vietnam	ND	N	500	N	3	No English
V7	Vietnam	ND	N	500	N	3	Crocus cream
C1	China	>8000	Y	1200	Y	5	No English
C2	China	ND	N	1200	Y	5	No English
C3	China	ND	N	4500	N	5	Natural plant essence
T1	Taiwan	>8000	Y	4000	Y	25	Acme,Vit. E
T2	Taiwan	ND	N	8000	N	6	Detailed warnings
U1	Unknown	ND	Y	4000	Y	12	Pearl and mink oil
U2	Unknown	>8000	N	4000	Y	12	Natural extracts
A1	U.S.	ND	Y	12000	Y	90	Vit. E, Aloe Vera
A2	U.S.	>8000	N	1200	Y	4	Vit. E, Pearl powder

Hg is μg/g, Export* = for export only, Price in Riels and 4000 Riels = 1 USD, Bar is bar code, Size in grams.

Table 3. Replication with mercury kit.

Sample	Country	# Replicates	# with high Hg
Th1	Thailand	3	1
Th2	Thailand	3	1
Th3	Thailand	4	2
C1	China	5	2
V1	Vietnam	5	4
T1	Taiwan	3	3

Replicates is number of replicates, # with high Hg is the number of replicates with >2000 μg/g Hg.

replicates within the screening kit's detection limit (Table 3). Using identical splits of samples collected in 2007, the kit and CVAA results were consistent, indicating that the test kits were accurate within the listed range. However, some of the results of replicated products collected in 2008 indicated some heterogeneity. In two sets of Thai whiteners (Th1, Th2) processed in triplicate, only the samples collected in 2007 tested positive for mercury (Th1 >8000 μg/g, Th2 >2000 μg/g). In four replicates of Th3, the sample from 2007, and two from 2008 had >2000 μg/g mercury while one from 2008 did not appear to contain elevated mercury. Likewise, in a set of five samples of C1 (the 2007 sample apparently from China with the very highest mercury), the sample collected in 2007 had >8000 μg/g mercury, only one of two collected in 2008 had >2000 μg/g mercury and the two collected in 2009 did not have detectable mercury. However, four of five samples of V1 (apparently from Vietnam) contained >2000 μg/g Hg.

In the samples collected in 2008, one packaging (T1) looked very much like V1 (Vietnam), but the label claimed it was produced in Taiwan so in 2009 we collected and processed it in triplicate; all three samples tested as >8000 μg/g mercury. The "American" whitener with high mercury (A2) was also suspicious in that the labeling was written in weak English. These were the only examples of suspicious labeling that might indicate copies. In a study of medical drugs in this region, packaging of counterfeit drugs was very professional and difficult to distinguish from legal products (USAID 2008).

The quality of the labeling of the skin whiteners varied greatly. The only consistency was the lack of any Khmer. English is used as a second language, but there was often too little English on these labels. A few gave detailed warnings of potential problems and provided advice on their use. None of the creams collected in 2007 reported mercury content. In 2008, one cream said it did not contain mercury and it indeed did not contain detectable levels of mercury. Bar codes were not used consistently. There was no relationship between the use of a bar code and mercury content. Five of the 16 skin whitening products without bar codes contained >2000 μg/g Hg (31%) and 6 of the 25 skin whitening products with bar codes contained >2000 μg/g Hg (24%). Note that some of these inexpensive creams likely also contained hydroquinone or retinoic acid (Farrell 2007), other toxic whiteners, but they were not listed on the labels either. These creams were collected from four popular public markets. Similar products at the major department stores or

boutiques selling mainly to foreigners or richer Khmers were not sampled, but our results apply to most Khmers who shop in inexpensive markets.

The skin creams that were purchased were almost always in jars containing 3 to 6 grams. The small size enables the vendors to sell these creams for an average price of 1990 riel (±1390) or about $0.50 U.S. The modest price makes these creams affordable to many women in the city. Mercuric compounds are relatively cheap at about $24 a kilo (Farrell 2007). Thus the cost of mercury in sample C1 with the most mercury was less than $0.0014 U.S. The mercury whitening ingredient in these skin creams cost less than 0.4% of the retail price.

Skin Concoction Supplements

It is a common practice in Cambodia to mix different skin whiteners into a personal concoction. In 2007, one product sold as a whitener (C2, Table 1) was actually an antifungal treatment and only had one word that was not Chinese—"ketoconazole." In 2008, seven vendors sold us five products containing powerful steroids (sometimes containing antibiotics) to mix with skin whiteners to enhance the whitening effect (Table 4). In 2008, another six vendors sold three products without steroids that contained antifungal or antiseptic properties to mix with skin whiteners (Table 4). The antibiotics and corticosteroids would require a prescription in many countries. The products with English gave ample warnings such as "the most powerful corticosteroid in combination with the antibiotic Neomycin" and recommended medical supervision. Some products had very little English. None of these products had any labeling in Khmer and it did not seem that most of the vendors or customers knew what these non-whitening products were. They responded to word-of-mouth advice that these products should be added to concoctions to get better whitening.

DISCUSSION

To manage this mercury problem in Cambodia requires an understanding of the toxicity of skin creams, the potential for control of these products in Cambodia, and how international efforts might mitigate the abuse. The evidence for mercury toxicity from use of some skin whiteners is comprehensive. Weldon *et al.* (2000, p. 17) reported on users of a skin cream with elevated mercury showing the following symptoms; "fatigue (67%), nervousness and/or irritability (63%), severe headaches (61%), insomnia (51%), memory loss (44%), loss of strength in legs (44%), tingling or burning sensations (39%), tremors or shaking of the hands (38%), depression (31%), and a metallic taste in the mouth (20%)." The World Health Organization (WHO) (2003) reviewed publications on skin creams with elevated mercury showing nephrotic syndrome or impaired renal function. Counter and Buchanan (2004) expressed their concerns that pregnant women who use skin creams with mercury could cause neurological, nephrological, and dermatological damage in their fetuses.

In general, renal and nervous system damage is expected from significant exposure to inorganic mercury (Clarkson and Magos 2006). WHO (2003) also reviewed other toxicity symptoms from inorganic mercury such as behavioral disorders,

Table 4. Non-whiteners sold for use with whiteners.

Type	Country	Ingredient	Price	Bar	Size	Comments	#
Steroid antibiotic	India	Fluocinolone acetonide neomycin	2500	Y	15	Medical supervision	2
Steroid	China	Fluocinocide	500	N	10	Many warnings	2
Antifungal	China	Ketoconazole	1500	Y	7	1 word not Chinese	3
Steroid antifungal	Thailand	Betamethasone clotrimazole	2500	Y	5	Mostly Thai	1
Steroid antifungal antibiotic	Vietnam	Betamethasone clothrimazole gentamicin	3000	Y	10	Warnings prescription only	2
Steroid antibiotic	Vietnam	Dexamethasone cloramphenical	1300	N	8	Apply thin <8 days	1
Antiseptic antifungal	Vietnam	Resorcin miconazole	6000	N	6	Minimal English	1
Antiseptic	Vietnam	Chlorhexidine	600	Y	6	Export only	1

Size in grams, price in Riels, Bar = bar code, # is number of markets bought at.

irritability, memory disturbances, and suppression of immune system that might also apply to skin creams. Psychological evaluations of miners exposed to elemental mercury have potential relevance too. Grum *et al.* (2004) reviewed emotional and personality changes in former mercury miners such as depression, introversion, and a tendency for an interaction with alcohol enhancing depression.

Risk Assessment

Compared to the extensive literature available for risk assessment on oral consumption of mercury (primarily in conjunction with eating fish), relatively little data are available to calculate risk assessment for dermal exposure. The U.S. Environmental Protection Agency (USEPA) has published reports on dermal absorption of mercury from water and soil, but there seems to be no concurrence on the absorption fraction for mercury in soils or skin creams. With respect to dermal absorption, the New Jersey State Department of Environmental Protection states "Additionally, few inorganics, other than cadmium and arsenic, have sufficient data to develop reasonable default values" (NJDEP 2008, p. 3).

Mercury and cadmium have the same permeability coefficient for dermal absorption (0.001, USEPA 2001) and although mercury is absorbed more readily orally than cadmium, a conservative approach for a scoping analysis would be to use 0.001 as the dermal adsorption fraction for mercury. However, skin creams are designed to enhance dermal absorption. Many details of skin creams are proprietary, but the U.S. patent office has approved patents based on a "benzoyl peroxide composition having enhanced bioavailability and percutaneous absorption" (Scott *et al.* 1988, p. 1). Bootleggers of such products start with patent searches and they seem quite effective at their "art." When lipophilic compounds with the capacity to complex mercury are added by a producer of a copy-cat whitener using mercury or when mixed with a concoction containing mercury, absorption of mercury is very likely enhanced.

Other uncertainties with copy-cat products or concoctions include the effect of nanoparticles on enhanced absorption of mercury (Little *et al.* 2007). If nanoparticle technology were copied from brand-name producers of cosmetics and combined with mercury to enhance whitening, likely nanotechnology would increase mercury absorption. Seven vendors sold us five skin cream products containing steroids including corticosteroids and six vendors sold us three products containing antibiotics and disinfectants to mix with skin whiteners. It is not clear what effect these ingredients in concoctions have on mercury assimilation, but again, these products contain compounds to help deliver the drugs through the skin and may enhance mercury assimilation. Olumide *et al.* (2008) observed serious damage to kidney, skin, immune, and endocrine systems and even death as the result of using concoctions of skin lightening products containing corticosteroids. Mahe *et al.* (2003) also found that the most serious damage from skin whiteners was associated with powerful corticosteroids. Until demonstrated otherwise, it is prudent to also consider a higher absorption fraction such as has been observed in animals. Friberg *et al.* (1961) and Skog and Wahlberg (1964) observed that 2% to 4.5% of mercury chloride was absorbed through the Guinea Pig skin.

There is uncertainty about the fraction of mercury adsorbed at various doses of mercury, but Iman *et al.* (2004) who evaluated skin whiteners with 0.316 μg/g and

71063 μg/g stressed "the potential harm of these mercury containing skin-lightening creams regardless of their mercury contents especially for women who apply these creams frequently or for extended periods." Afonne *et al.* (2002) also discovered that low dose oral mercury exposure (*i.e.*, 4 μg/ml) in mice produced necrosis and widening of the golmeruli. In consideration of the uncertainties associated with enhanced dermal absorption as well as an absorption fraction of 0.001 we will also evaluate risk with an absorption fraction of 0.03 similar to that absorption reported in Guinea pigs.

Another uncertainty is the proportion of the body that is treated with skin whiteners. Mahe *et al.* 2003 reported that in their study 92% of African users (n = 425) covered their entire body with whitening cream. A mean total female body surface is 16,000 cm^2 (Bender 1995). It seems from our simple interviews that most Khmers treat only their face, which has a surface area of about 9% of the whole body or 1440 cm^2 (Sheng *et al.* 2003). For simplicity of demonstration only facial treatments were evaluated.

A reference dose is the U.S. Environmental Protection Agency's (USEPA's) maximum acceptable dose of a toxic substance. The reference dermal dose ($RfD_{ABS,}$ USEPA 1995) can be calculated by multiplying the oral reference dose (mg/kg-day) (RfD_O) by the fraction of contaminant absorbed in the gastrointestinal tract (ABS_{GI}) (USEPA 2001). So with mercuric chloride or similar inorganic mercury compounds it becomes:

$$RfD_{ABS} = RfD_O \times ABS_{GI}$$

or

$$RfD_{ABS} = 0.0003 \times .07 = 0.000021 \text{ mg/kg-d}$$

Although many of the skin whiteners recommend applying in the morning and evening, simple interviews indicate that most Khmers only use the cream in the evening so our calculations are based on one application per day. Thus for those who followed the instructions on the packaging, we would under represent the dose by 50%. Also if we evaluated a whole body dose, the risk would be substantially greater. The essential parameters to calculate acceptable concentration of mercury in skin cream (C_{cream}) are reviewed in Table 5.

$$C_{cream} = \frac{THQ^*RfD^*BW^*AT^*365/d - yr^*10^6 mg/kg}{ED^*EV^*SA^*AF^*ABS_d}$$

With an absorption fraction of 0.001 and a hazard index of 1.0:

$$C_{cream} = 1 \times 0.000021^*45^*30^*365^*100000/(350^*370^*6.9^*0.001) = 1158 \ \mu g/g$$

or with an absorption fraction of 0.03 and a hazard index of 1.0:

$$C_{cream} = 1 \times 0.000021^*45^*30^*365^*100000/(350^*370^*6.9^*0.03) = 39 \ \mu g/g$$

Thus, using the conservative absorption fraction of 0.001 gives a dermal hazard index of 1158 μg/g; 11 of the creams we sampled exceeded the associated acceptable risk. However, it is highly likely that some skin creams and concoctions of skin treatments result in a much higher absorption fraction than 0.001 and the acceptable concentration of mercury in skin whiteners may be closer to 39 μg/g. If we were

Table 5. Variables used in risk analysis.

Parameter	Definition	Default adult female
THQ	Target Hazard Quotient	1
BW	Body weight (kg)	45
AT	Averaging time (yr)	30
RfD_{abs}	Reference dose (mg/kg-day)	0.000021 mg/kg-d
ED	Exposure Duration (yr)	30
EV	Event Frequency (events/day)	1
EF	Exposure Frequency (days/yr)	360
SA	Surface Area (cm^2)	1440[a]
AF	Adherence Factor (mg/cm^2-event)	6.9[b]
ABS	Absorption Fraction	.001 or .03

[a]Face surface area represents about 9% of the whole body (Sheng *et al.* 2003) and total surface area of female is about 16,000 cm^2 (Bender 1995).
[b]A typical woman uses about 10 ml of whitening cream a day and we assume only the face is treated (10000/1440) (http://www.alibaba.com/catalog/101274379/Fv4_Helichrysum_Night_Cream_50ml.html).

to assess whole body treatment or use of these products in children, the estimate approaches the 1 μg/g standard for skin whiteners set by the U.S. Food and Drug Administration and the ASEAN.

Comparisons to Existing Medical Reviews

Although mercury in skin creams is clearly capable of causing various medical problems, it is not clear that the concentrations of mercury in these skin creams purchased in Phnom Penh did cause significant toxicity. Extrapolation of published studies is limited by aspects such as the more extensive medical evaluations were done with skin creams with more mercury than we detected (*i.e.*, 60,000 μg/g Hg, Barr *et al.* 1972; 80,000 μg/g Hg, Weldon *et al.* 2000). Recently, a woman in New York who had used a skin cream with 6000 μg/g mercury (less than the two most contaminated whiteners in our study), required medical treatment (Heyward 2005; Leighton 2005). Also a woman in Hong Kong was reported to have kidney damage associated with use of skin whitener containing 2000 μg/g mercury (Soo *et al.* 2003). Studies by Agusa *et al.* (2007) suggest that mercury toxicity in Phnom Penh is occurring. Agusa *et al.* (2007) observed that high mercury levels in hair (0.69–190 μg/g dry wt) and blood (5.2–58 μg/l), in Phnom Penh correlated with increased serum estrone and estradiol levels. Agusa *et al.* reported in 2005, three of 60 hair samples from urban areas in Phnom Penh contained >50 μg/g, which are levels associated with neuropathy (WHO 1990) or Minamata disease (Harada 1995). Another seven of their hair samples from urban areas were greater than 10 μg/g, levels associated with neuropsychological dysfunctions in children (Grandjean *et al.* 1997, Grandjean *et al.* 1999). It is quite likely that Agusa's results reflect use of skin creams. Extrapolation of current data is uncertain and the degree of mercury toxicity in Phnom Penh from skin whiteners is not obvious, but clearly more evaluation of mercury toxicity in Phnom Penh is warranted.

Ideally actions should attempt to resolve the problem while analyzing it in more detail. Education associated with medical aid has been effective in both developing and advanced countries. Barr *et al.* (1972) ran medical clinics in Kenya to treat nephrotic syndrome caused by mercury in skin whiteners. The kidneys of half of their patients quickly recovered and much of the treatment effect was related to educating them to stop using skin whiteners. Medical clinics with similar education were also held in the United States when mercury contaminated whiteners were discovered (Weldon *et al.* 2000). Protein and mercury analysis of urine could be done in Phnom Penh to resolve if kidneys were being damaged by mercury. Analysis of hair for mercury would be a small addition that would clarify the uncertainty of mercury contamination in Phnom Penh, but urine analysis should be the first priority. The potential for behavioural disorders from mercury could be resolved with minimal equipment, but the professional evaluation is complex and the educational aspect is less obvious. The immune system is weakened by mercury (WHO 2003), but attempts to resolve associations between disease and mercury in Cambodia would likely be complex and expensive although a nice aspiration.

Any medical clinics would have to be simple and education should be a key component. Avoiding the use of any skin whitening is the best treatment. Such clinics could include analysis of more skin whiteners so that the public could avoid the most contaminated products. At least for screening purposes, future analysis should consider using a less sensitive approach than a cold vapor atomic absorption spectrophotometry system dedicated to mercury analysis. Such sensitive equipment is best for validation. Contamination by the most elevated of the skin cream samples required extensive cleaning of the instrument. In Dec 2007, ASEAN suggested a screening method that should enable a more complete analysis of the market (ASEAN Cosmetic Committee (ACC) 2007). The screening kit we used is effective in detecting the creams with the highest mercury concentrations that would contaminate equipment and it can provide a focus on the most hazardous creams. But it is not clear that this kit is sensitive enough to detect all samples with toxic levels of mercury. Moreover, because it requires a large sample size (3 g), most jars of cream are 3–5 g in size, and mercury concentration is variable, this kit could not provide an individual much screening ability.

International Implications

Like most developing countries, Cambodia is very dependent upon foreign aid and international efforts are required to control mercury (Irvine *et al.* 2006). Cambodia is amongst the poorest countries in the world, ranking 131 of 177 countries in the 2007/8 Human Development Index (http://hdr.undp.org/en/). The GDP per capita in 2007 was $571 (http://www.state.gov/r/pa/ei/bgn/2732.htm). The Khmer Rouge killed or forced most educated people into exile. Not only did the Khmer Rouge period exact a heavy toll on the Cambodian population, there also were major impacts on institutions and infrastructure within the country. Universities were closed, as were many primary and secondary schools. Phyrun (1996, p. 1) noted that one of the outcomes of the Khmer Rouge (KR) period was the "complete destruction of institutions responsible for management of the country's resources." The impact of the KR goes beyond the years when they ruled Cambodia (1975 to

1979). To suppress the KR, Vietnam occupied Cambodia from 1979 to 1989. Murders of tourists by KR continued into the mid 1990s, thus forcing a high proportion of government funding to be spent on security. In 2009, Cambodian government funding on health and education was assessed as the lowest observed in an international review by an international survey funded by Canada (Center for Economic and Social Rights 2009).

The problems in Cambodia go beyond the destruction of medical, educational and scientific agencies by the Khmer Rouge. Problems with accountability, transparency, and legal enforcement continue to persist in Cambodia (Lum 2007). In January 2008, Cambodia agreed to adopt the ASEAN cosmetic standards. Moreover, in August 2008, a subdecree was passed banning importation of products not following ASEAN cosmetic standards (Chhay 2008). It is essential that ASEAN partner countries work both within their borders and collectively as an association, to eliminate the production of mercury-containing products. This will require a serious and coordinated effort by responsible governments.

The financial incentive to make counterfeit cosmetics is huge. No surveys exist for Cambodia but regional surveys reflect the market for the producers of the skin whiteners. In 1999, the Japanese market for skin whiteners exceeded $5 billion (Glenn 2008). Surveys in 2004 and 2007 estimated the proportion of women regularly using skin whiteners as follows: Japan and Hong Kong 18%, Taiwan 20%, China 30%, and Philippines 50% (Glenn 2008). It is not clear who makes mercury containing products sold in SE Asia. However, it seems that production of some products labeled "for export only" represents an intentional action to allow production of products not legal for sale in the country of origin. The Food and Drug Administration of Thailand (FDA 2002) considers mercury a prohibited substance that "must not form a part of cosmetic products except under the conditions laid down" (Thailand Cosmetic Act 1992). Similarly, skin creams with mercury are illegal to sell in the European Union (EU), but in spite of lawsuits, it is very well documented that they are made for export there (Glenn 2008). The export of mercury and mercury compounds from the EU will be prohibited from March 15, 2011, http://www.europarl.europa.eu/news/expert/infopress_page/064-29478-140-05-21-911-20080520IPR29477-19-05-2008-2008-false/default_en.htm.

In the United States, a bill was passed into law October 2008 by both houses of Congress to ban the distribution and export of mercury. Sponsored by then-Senator Barack Obama, the Mercury Export Ban Act of 2008 will take full effect January 1, 2013. The new law further requires an extensive Report to Congress on "mercuric chloride, mercurous chloride or calomel, mercuric oxide, and other mercury compounds, if any, that may currently be used in significant quantities in products or processes." As export bans take effect in the European Union and the United States, the world trade in mercury should decrease significantly. It is still important to restrict trade in other countries that are yet to prohibit sales of mercury containing cosmetics. Attention must be directed at countries exporting toxic cosmetics to countries like Cambodia with limited capacity to control such trade.

New ASEAN regulations on cosmetics including skin whiteners were implemented January 1, 2008 (Steinberg 2008). Our observations of skin creams in several markets in Phnom Penh in July and December of 2008 do not indicate compliance of

labeling as required in the new regulations. It is not certain if manufacturers are complying with the new regulations or if distributors are selling old stock. It was not possible for us to estimate the volume of sales of mercury containing products. Some vendors admitted they sold counterfeit copies but would not discuss details or sell us these products. We can only state that toxic levels of mercury were present in >27% of brands of skin whiteners in popular markets in Phnom Penh. In the summer of 2008, similar looking whiteners were observed in many parts of Cambodia (Battambang, Pursat, Siem Reap, Sihanoukville, *etc.*) and Bangkok, Thailand. In 2007 these creams were not available in remote sites such as tribal areas of northeast Cambodia (Ratanakirri). It is important to expand upon the work we did in simple markets, look for counterfeit creams in more upper class markets and process samples from other regions.

Two other regional examples illustrate that the chances of export of mercury containing creams to Cambodia being random are very slight. According to official regulations in Taiwan, mercury salts are forbidden as a bleaching agent in cosmetic products. In a sampling of 80 brands of skin whiteners in Taiwan, only one had significant mercury (Lin *et al.* 1999). Unlike Cambodia, Taiwan monitors such creams and vendors avoid marketing mercury containing creams. In another example in 2000, a study of 38 skin-whitening creams in Hong Kong showed eight made by global cosmetic makers exceeded the U.S. Food and Drug Administration safety limits for mercury (Chan *et. al.* 2001). After media attention and official action, two years later a 2002 Consumer Council study found that all 32 skin-whitening products tested passed the safety requirement for mercury (Wong 2004).

CONCLUSIONS

Many women in Phnom Penh are using skin whiteners with toxic concentrations of mercury. Unfortunately, official action in Cambodia does not seem imminently likely to control this contamination. In surveys of medical drugs in Cambodia anywhere from 30% to 100% of products were counterfeit or at least misrepresented on the labels (USAID 2008). Since very little mercury is required to make skin whiteners, the concept of increasing the price of mercury to suppress use of mercury by artisanal miners does not apply well to skin whiteners. International efforts to restrict production and export of skin whiteners should continue. Medical clinics as were done by Barr *et al.* (1972) and Weldon *et al.* (2000), focusing on kidney and other damage from mercury, funded with international aid and augmented by education are likely the most effective strategies.

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