APPENDIX D

ESTIMATION OF POTENTIAL INTER- AND INTRA-INDIVIDUAL VARIABILITY FOR HUMAN RESPONSE TO HG VAPOUR EXPOSURE

A number of recent publications have examined factors relating to human variability in urinary Hg levels following inhalation exposure. Data have been gathered from occupational exposure studies, with no information being identified to characterize the variability based on exposure to the general population via ambient air. Several factors play a role in the variability in humans, including daily exposure levels, duration of exposure, and pharmacokinetics/ pharmacodynamics. Symanski et al. (2000) examined the variability in urinary Hg levels as a result of exposures related to activities at a chloralkali plant. The study noted that substantial variability was due to day-to-day variation in airborne Hg levels. Suzuki et al. (1992) reported that acute exposures to Hg have been linked to a longer elimination half-life compared to the half-life from chronic, long-term exposures. Therefore, the nature of the exposure to Hg can result in variable Hg concentrations in the urine of exposed individuals. The European Union (EU, 2001) concluded that a good correlation between urinary Hg values and the concentration of Hg in air has only been demonstrated following stable exposure and correction of the urinary Hg values for the urinary excretion rate and normalization to the time elapsed following exposure.

The available literature was reviewed for studies that report Hg vapour concentrations and associated urinary Hg levels. These studies are summarized in Table 1. To the extent possible, the data has been sorted by exposure duration and exposure level. Urinary levels of Hg are reported in either µg Hg/L urine or µg Hg/g creatinine in the urine. Data from a number of these studies has been used to fulfill our ultimate objective of this task, i.e., a quantitative assessment of the inter-individual variability and characterization of the uncertainty associated with inter-individual variability. In addition, the data were examined in light of intra-individual variability and include an analysis of factors affecting urinary Hg levels as a function of Hg vapour concentrations.

When individual urinary Hg measurements are available the inter-individual and intra-individual variability can be estimated using analysis of variance (Symanski et al., 2000). Unfortunately, these data are rarely available in published studies. Instead, summary statistics, such as mean urine levels across multiple individuals are reported in the literature. This necessitates a different approach to determine inter-individual and intra-individual variability in Hg response. Furthermore, it can be difficult to distinguish between inter- and intra-individual variability in these studies if factors such as the variability in Hg exposure, type of work performed by the individual, use of spot or composite urine samples, time of urine collection, and other factors are not accounted for in the studies. Typically, any of the reported variability includes a combination of intra- and inter-individual variability. For this report, provided that the study was able to minimize the contribution of intra-individual variability – such as by using composite urine samples, average air Hg concentrations, and workers in known job activities - the variability was considered to be dominated more by inter-individual variability. If spot

urine samples were collected over different times of the day for a given individual, and the individual results are provided in the studies, then the variability may be dominated by intra-individual variability.

A multiple lines-of-evidence approach was taken to estimate the potential inter-individual variability for human responses to Hg vapour exposure. Most studies available in the published literature focus on industrial exposures (e.g., chloralkali workers). Since these exposures are greater than that expected for typical environmental exposures, a key initial assumption is that the behavior of Hg in individuals exposed under industrial exposures would be representative of its behavior under more “dilute” conditions. This assumption is reasonable provided that the industrial Hg exposures would not represent toxic levels that would affect the normal behavior of organ systems and excretion mechanisms during exposure.

Our analysis assessed the following:

- the variability in the relationship between urinary Hg concentrations and Hg air concentrations; and

- the variability in the pharmacokinetics of Hg in humans.

This analysis is presented in the subsections below.

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
ATSDR (1999)	9 Healthy Volunteers (2 Male, 7 Female	1 % of the *absorbed* Hg excreted via the urine during the first 3 days. 8-40% excreted during the 30 days after exposure.		400 µg/m3 (365 - 430)	15 minutes	
ATSDR (1999)		Mean total Hg in the general population 4-5 µg/L				Baseline measurement
ATSDR (1999)		>2 µg/L		0.016 - 0.68 mg/m3		Stopford et al. (1978)
Bell et al. (1973)	4	70-154 (Mean 112) µg/L		73.1-151 µg/m3 (Mean 107)	8 hr over 5 days (TWA)	16 hr composite sample on Friday; Cited in Tsuji et al. (2003)
Boogard et al. (1996)	Workers producing Natural Gas - High	High group - 23.7; Low group - 4.1; Control group 2.4 µg/g	High group - 17 Low group - 5 Control group 2 µg/g	10 - 1500 µg Hg/m3, (Median = 67 µg Hg/m3)	8 hours	
Borjesson et al. (1995)	20 Occupationally exposed workers	20 workers: range 17-96; Mean 59	10-69; Mean = 34 µg/g	Not clearly given. States that levels similar to 30 µg/m3	1-24 Years; Mean = 8.6	Vapour concentration reference taken from Sallsten et al. (1990, 1992).

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
		Referents: range 0.3 - 4.1; Mean 2.2 µg/24 hours	0.2-3.9; Mean 1.7 µg/g	have been found at the chloralkali plants and the thermometer factory from which the subjects were recruited.		
de Burbure (2003)	Residents living near a known to be contaminated non - ferrous smelter		89 boys - 0.03-18.6 ; Mean 0.93 85 Control - 0.02-25.7 ; Mean 0.99 87 girls - 0.03 - 18.6 ; Mean 1.18 155 men: 0.05-7.58 ; Mean 0.55 91 Male Controls 0.05-41.2 ; Mean = 0.56 165 women - 0.04-13.11 ; Mean = 0.59 82 Female controls - 0.07-7.03 ; Mean = 0.75			(8.5-12.3 years-old) (8.5-12.3 years-old) (18-51 years-old) (18-51 years-old) (18-54 years-old) (19-50 years-old)

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
			78 Control (girls) - 0.03 - 22.4 ; Mean 0.89 µg/g			(8.5-12.3 years-old)
DeRouen et al. (2002)	41 8-10 year olds with and average of 6.1 carious teeth four of which were permanent)	Group 1 - Average 1.42 µg/L Group 2 - Average 1.54 µg/L Median Hg level of 2.0 µg/L				Baseline urinary Hg levels taken from children. Baseline urinary Hg levels taken from children. Background Hg levels
Ellingsen et al. (1994)	Occupational Workers		76 Male workers - 0.3 - 6.1 (1.8) 53 Referents - 0.3 - 3.8 (1.3) nmol/mmol		1.1 - 36.2 years	ages 24.2 - 64.8 ages 24.3 - 63.7
Ellingsen et al. (2000)	Occupationally exposed workers		47 exposed workers 1.1-16.8 (ave = 5.9) 47 Referents 0.2 - 5.0 (ave = 1.3) nmol/mmol		2.8 - 34.5 years (ave = 13.3)	Ages 24-66 Ages 23.3-64.2
Fawer et al. (1983)	Occupationally exposed workers		26 exposed workers - 11.3 25 Referents - 3.4 µmol/mol Cr	0.026 mg/m3	Mean 15.3 years	Average age 44 years Average age 44 years
Frumkin et al. (2001)	Former Chloralkali plant workers	78 workers: 13.0 - 172.7 (Mean 72.1)			4 Years (1998 - 1991)	Corrected to a specific gravity of 1.024

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
		147 workers: 3.42 (s.d. 2.54) Control group: 3.12ug/L (s.d. 2.48) µg/L	2.76 (s.d. 2.04) 2.31 (s.d. 1.89) µg/gm		(Mean since last exposure = 5.7 years)	
Haut et al. (1999)	13 Men	Not determined		80 ug/m3	2 - 4 weeks	
Hsu et al. (1999)	Male Shipyard worker	248.8 µg/L		0.75 mg/m3*	8 - hrs	48 years-old (Industrial hygiene monitoring of Hg vapour in air during simulated flamed cutting of the steel plates showed levels exceeding 30 times the PEL of 0.025 mg/m3, or 0.75 mg/m3 as shown)
Kobal et al. (2000)	45 previously exposed miners (ages 24 - 50, ave 37)		45 workers pre-exposure: Mean 18.5 45 workers post-exposure: Mean 69.9	0.05 - 0.73 (0.36) mg/m3 (TWA)	6 - 82 days (Mean 37)	(ages 24 - 50, ave 37)
			23 Miners with normal pattern of urinary proteins Pre-exposure 4-40; Mean 19.7±9.9; Median 20			

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
			23 Miners with normal pattern of urinary proteins Post-exposure 23-138;Mean 62.4±43.62; Median 49			
			15 Miners with HMW pattern of urinary proteins pre exposure 4-42; Mean 19.0±10.0; Median 19.0			
			15 Miners with HMW pattern of urinary proteins post-exposure 27-192;Mean 70.9±43.98; Median 54			
			7 Miners with LMW pattern of urinary proteins pre exposure 6-23; Mean 13.4±7.76; Median 11.0			
			Miners with LMW pattern of urinary proteins post-exposure 44-171;Mean 92.3±48.09; Median 101 µg/g			

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
Liang et al. (1993)	Occupationally exposed workers:	88 workers: 0.024±0.058 mg/L		0.008 - 0.085 mg/m3 (Mean 0.033 mg/m3)	At least 2 years (work day shifts)	24 hour urine analysis; 69 male, 19 female; 46 male control, 24 female control
Lindstedt et al. (1979a) Study I	13	76-307 (Mean 162) µg/L		34.3-111 ug/m3 (Mean 63.3)	Static Samples; daily for two weeks (TWA)	Spot samples (not SG corrected) daily (post shift) for 2 weeks; Cited in Tsuji et al. (2003)
Lindstedt et al. (1979b) Study II	15	23.4 - 65.4 (Mean 39.1) µg/L		14.7 - 43.0 ug/m3 (Mean 23.0)	Personal samples; daily for 8 weeks (TWA)	Spot samples twice a week for 8 weeks (post shift); Cited in Tsuji et al. (2003)
Lodenius and Malm (1998)	21 gold shop workers (Alta Floresta region)		Mean = 160 µg/g	0.07 - 41 µg/m3 (Mean 5.1µg/m3) at dealers shops (reburning sites).		
Mattiussi et al. (1982)	21	10.8 - 50.4 (Mean 25.6) µg/L		6.1 - 37.8 µg/m3 (Mean 16.7)	Static Samples over 1-3 years (TWA) reported as identical to personal sampling	Sample type and duration not specified; Cited in Tsuji et al. (2003)
Moszczynski et al. (1995)	Occupationally exposed workers	26 (21-49 year-old) males (I): range 0 - 240		26 (21-49 year-old) males (I): range 0.024 - 0.09 mg/m3 (TWA)	Under 10 years (Ave. 3.35 ±1.77)	Peak Hg Concentrations per shift varied between 0.05 and 0.32 mg/m3 from 1968-1993
		55 (31-35 year-old) males (II): range 0 - 240 µg/L		55 (31-35 year-old) males (II): range 0.024 - 0.09 mg/m3 (TWA)	10- 31 years (Ave. 19.9 ± 5.8)	Peak Hg Concentrations per shift varied between 0.05 and 0.32 mg/m3 from 1968-1993
Moszczynski et al. (1995)	Control: 36 males (28-55 years-old)			No history of exposure	No history of exposure	

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
	15	17.8 - 115 (Mean 58.0) µg/L		28.7 - 128 µg/m3 (Mean 54.5)	Personal samples for 8-9 hr over 10 days (TWA)	Four samples (SG corrected = 1.017) over a day; Cited in Tsuji et al. (2003)
Netterstrom et al. (1996)		Lo: 28.8 - 48.0 (Mean 35.2)		0-0.15 mg/m3	Acute	
		Hi; 49.5 - 249 (Mean 106.5)		0-0.15 mg/m3	Acute	
		Control: 4.5 - 14.1 (Mean 10.5) (nmol/L)		0	None	
Nordhagen et al. (1994)	34	31.0-251 (Mean 92.3) (µg/L)		13.4-191 µg/m3 (Mean 61.9)	Static samples; twice a week at 130 points. Annual means 1953-1987 based on quarterly means	Quarterly samples (type and SG correction not reported); Cited in Tsuji et al. (2003)
Park et al. (2000)	20 Workers (lamp makers)	1.8 - 163.5 (µg/L)		0.0041 mg/m3 (Shift weighted TWA)	4 - 62 months (Mean 31 months)	
Piikivi and Tolonen (1989)	Workers from chloralkali plant		41 Male workers: 2.1 - 31.2 (Mean 11.6) 41 Controls: 0.0 - 2.9 (Mean 1.1) µmol/mol Cr	25 µg/m3	5- 27 years (Mean 15.6 years (S.D. 8.9))	28-55 years old (Ave 38.1 yrs). One age matched referent found for each exposed worker

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
Piikivi and Hanninen (1989)	Exposed workers (n = 60)	15 - 260 (Mean 84.1) 5 - 30 (Mean 10.0) (nmol/L)	60 workers: 1.9 - 31.2 (Mean 10.1) 60 Referents: 0.6 - 3.8 (Mean 1.2) µmol/mol Cr			
Piikivi (1989)	Chloralkali workers		41 Male workers: 3.5 - 52.5 (Mean 19.3) 41 Controls: 0.0 - 4.6 (Mean 1.8) µg/L	"about 30 µg/m3"	5- 27 years (Mean 15.6 years (S.D. 8.9))	28-55 years-old. (Ave age 38.1 yrs)
Queiroz et al. (1994)	Workers from a Hg producing plant		44 Males: 3.5 - 67.9 µg/g	No Concentration Given	3 - 46 months	Distribution : 12 workers <10 ug/g; 10 workers; 10-20 ug/g; 7 workers 20-30; 3 workers 30-40 ug/g; 8 workers >50 ug/g
Queiroz and Perlingeiro (1995)	Workers from a Hg producing plant		48 Males: 1.0 - 97.4 µg/g		0.5 - 46 months	Distribution : 15 workers <10 ug/g; 12 workers; 10-20 ug/g; 6 workers 20-30; 3 workers 30-40 ug/g; 8 workers 40-50 ug/g; 4 workers >50
Risher et al. (2003)	4 children exposed to two vials of liquid Hg taken home from a classroom One vial was spilled in a van.	40 - 428 µg/L		53 µg/m3 - 1.764 mg/m3 (conc. in the home); 26 - 287 µg/m3 (conc. in the van)	3 months	

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
Roels et al. (1987)	10	13.4 - 100 (Mean 51.5) µg/L	Theoretical result = 61 Cr µg/g	15.7-89 µg/m3 (Mean 40.9) 50µg/m3	Personal samples; 6hr over 5 days (TWA)	9 a.m. spot samples for 5 days Also referenced in ATSDR; Ratio Hg-air (ug/m3):Hg-B (ug/dl whole blood): Hg-U/(ug Cr)
Smith et al. (1970)	18	68.2 - 773 (Mean 255) µg/L		3.5 - 272 µg/m3 (Mean 102)	Static samples collected six times a year (TWA)	Unspecified sample type four times per year; Cited in Tsuji et al. (2003)
Solis et al. (2000)	Family acutely exposed to Hg as result of home gold ore processing	45 day old infant: 24 hr urine = 35; Spot urine = 45 13 month old: 24 hr urine =120; Spot urine = 190 38 year-old Female: 24 hr urine = 163; Spot urine = 682		0.193 mg/m3 0.193 mg/m3 0.193 mg/m3	Not known. Acute exposure as result of home gold ore processing.	

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
		58 year-old Male: 24 hr urine = 112; Spot urine = unk		0.193 mg/m3		
		3 year-old: 24 hr urine = 161; Spot urine = 210		0.193 mg/m3		
		7 year-old: 24 hr urine = 177; Spot urine = 110		0.193 mg/m3		
		10 year-old: 24 hr urine = 485; Spot urine = 575		0.193 mg/m3		
		14 year-old: 24 hr urine = 107; Spot urine = 27 µg/L		0.193 mg/m3		
Stopford et al. (1978)	10	27.4 - 730 (Mean 183) µg/L		24 - 289 µg/m3 (Mean 82)	Personal samples over 5 days	Spot samples (SG corrected = 1.021) for 5 days (mid shift); Cited in Tsuji et al. (2003)
Stromberg et al. (1999)		5 - 75 nmol/L		25, 50, 100, 200 µg/m3 in succession	5 minutes (10 minutes - 200 ug/m3)	
Symanski et al. (2000)	955		10±9 µg/g	56 ug/m3	7 years	

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
Urban et al. (2003)			0.15 - 61.7 (Mean 20.5 ± 19.3) µg/g	59 µg/m3 (TWA)	3-33 Years (Mean 14.7 ± 9.7 years)	
Vimercati et al. (2001)	Occupationally exposed workers	19 workers: Current = 9.7 ± 5.5 (mean ± S.D.) (range 4-25); Cumulative = 14µg/L - 272 µg/L, Mean 97.6 ± 62.0 µg/L		0.0007 - 0.021 mg/m3 9TWA) (Mean 0.0058 mg/m3)	4 hour static samples (Average working-life 16.4 years)	(Ages 27-57, Ave 40.3 years-old, 16.4 working-life yrs)
		25 Controls: 2.4 ± 1.2 (mean ± S.D.) (range 1-5) µg/L				(Ages 28-60, Ave 44.3 years-old, 16.6 working life yrs)
White et al. (1993)	Worker in thermometer factory	690 µg/L		No Concentration Given	3.5 years	
White and Sabbioni (1998)		Urine level found in Healthy Adults 0.5-10.0				Referenced in Sweet & Zelikoff. Toxicology and Immunotoxicology of Hg: A comparative review in fish and humans. Journal of Toxicology and Environmental Health Part B, 4: 161-205, 2001.

Table 1. Summary of Literature Relevant to Hg Vapor Concentrations And Associated Urinary Hg Levels

Study/Reference	Exposure Group *(n)*	Level of Hg in Urine	Hg Concentration via creatinine measurements	Hg Vapour Concentration	Duration of Exposure	Comments
Yamamura (1990)	9	25.0 - 145 (Mean 71.1) µg/L		14.0 - 22.0 µg/m3 (Mean 19.3)	Static samples over 4 days (TWA)	8 -hr samples (corrected to unspecified SG) analyzed for inorganic Hg; Cited in Tsuji et al. (2003)
Yeates and Mortensen (1994)	2 youth acute residential exposure	15 year-old boy - 1314 13 year-old girl - 624 µg/L		50 - 400 µg/m3 51 - 400 µg/m3	3 Months 3 Months	
Yang et al. (1994)	4 workers	Worker 1: 610 (24 Hour Urine)		0.945 mg/m3 (TWA) Room A	10 hrs/day - 5 years	
		Worker 2: 408 (24 Hour Urine)		0.709 mg/m3 (TWA) Room A	4 hrs/day - 1.5 years	
		Worker 3: 110 (24 Hour Urine, Spot Urine)		0.225 mg/m3 (TWA) Room B	8 hrs/day - 3 years	
		Worker 4: < 20 (24 Hour Urine, Spot Urine) µg/L		0.225 mg/m3 (TWA) Room B	8 hrs/day - 7 years	

Assessment of Urinary Hg Concentrations and Hg Air Concentrations

Urinary Hg concentrations (U-Hg) have been correlated to Hg vapour air concentrations (Air-Hg) in several industrial exposure studies. Unfortunately, not all of the published studies presented in Table 1 provide sufficient information on the potential inter-individual or intra-individual variability. In this section both individual studies and a combination of studies are used to derive an estimate of the potential inter-individual and intra-individual variability in the relationship between Air-Hg and U-Hg.

Single Study Evaluation

Of the studies reviewed, Lindstedt et al. (1979a,b), Mattiussi et al. (1982), and Mniszek (2001) provide sufficient information on the pairings of exposure and U-Hg data to allow examination of the regressions between these parameters.

Mattiussi et al. (1982) compared time weighted average Air-Hg and U-Hg in workers from five different chloralkali plants in Italy. The workers were divided into nine different job categories (not all categories were represented at each facility) and 38 to 106 workers were tracked at each of the facilities. Multiple urine samples and multiple air measurements were available in this study. Although the study did not provide information regarding when the urine samples were collected, the authors normalized U-Hg concentrations to a specific gravity of 1.024, which reduces some of the variability introduced by confounders[1]. Based on the mean values for U-Hg and Air-Hg reported by the authors for each plant and job category, the following regression was generated:

$$\text{U-Hg} = 1.181\ (\pm\ 0.252) \times \text{Air-Hg} + 5.832\ (\pm\ 4.726) \qquad r^2 = 0.834$$

where U-Hg and Air-Hg have units of µg/L and µg/m^3, respectively. The values shown in parentheses represent the product of the standard error and the t-statistic and can be used to calculate the upper and lower 95th percentile confidence limits. Although the confidence bounds could be used to estimate the potential variability in response at a particular exposure, the two sets of bounding estimates (one for the slope and one for the intercept) can make this combined analysis cumbersome. To resolve this, Monte Carlo capabilities of the program @RISK (Palisade, 2004) were used to combine the effects of the confidence bounds on these two terms to derive the confidence interval on the U-Hg for different Air-Hg exposure concentrations. The inputs to @RISK were the regression slope, intercept, and the corresponding standard errors of these estimates (2.258 for the intercept and 0.121 for the slope). Multiple Air-Hg concentrations were substituted into the regression equation to estimate the U-Hg concentrations based on the distributions of the slope and intercept. Additional inputs or assumptions included the following:

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[1] The confounders for U-Hg include the following: creatinine concentration, urine specific gravity, time of collection, "spot" versus composite sampling, number of amalgam surfaces in oral cavity, fish consumption, illness, and others (Ellingsen et al., 1993; Tsuji et al., 2003).

- a normal distribution was assumed for both the slope and intercept;
- the input Air-Hg air concentrations were 2.5, 5, 10, 15, 20, 25, 30, 35 and 40 $\mu g/m^3$; and
- 10,000 iterations were used.

The ratio of the 97.5th percentile and 2.5th percentile from this analysis was used to estimate the potential inter-individual variability. This ratio ranged from 1.5 to 3.1 (mean: 1.8) across the nine test Air-Hg concentrations.

Mniszek (2001) reported results from Hg monitoring of 17 chloralkali workers from two different facilities in Poland. Time-weighted average Air-Hg (reported as $\mu g/m^3$) and U-Hg (reported as µg/g creatinine) were provided for all 17 workers. Details concerning the urine sampling (e.g., start of day, daily composite, or random) were not provided by the author. The following regression was generated by combining the results from both chloralkali facilities:

$$\text{U-Hg} = 0.26\ (\pm\ 0.54) \times \text{Air-Hg} + 49.63\ (\pm\ 39.7) \qquad r^2 = 0.06$$

where U-Hg and Air-Hg have units of µg/g creatinine and $\mu g/m^3$, respectively. The regression coefficient is quite poor, capturing only 6% of the total variability. As a result this regression was not evaluated further, since it was not appropriate to quantify the potential inter-individual variability.

Lindstedt et al. (1979a,b) reported results from two U-Hg studies in chloralkali workers. In the first study, U-Hg (reported as nmol/L, uncorrected for specific gravity) was determined over a 2-week period from 13 male workers that had been exposed to an average Air-Hg concentration of 64 $\mu g/m^3$ (range: 36 to 112 $\mu g/m^3$). These workers ranged in age from 19 to 63 years and had worked at the facility from 0.5 to 5.5 years. In the second study, U-Hg (reported as nmol/L, corrected for specific gravity) was determined over an 8-week period from 16 male workers that had been exposed to an average Air-Hg concentration of 23 $\mu g/m^3$ (range: 15 to 43 $\mu g/m^3$). These workers ranged in age from 19 to 63 years and had worked at the facility from 1 to 7 years.

Our reanalysis of the data from the first study yielded the following regression equation, which differs from that reported by the authors[2]:

$$\text{U-Hg} = 6.92\ (\pm\ 8.35) \times \text{Air-Hg} + 365.79\ (\pm\ 562.21) \qquad r^2 = 0.23$$

where U-Hg and Air-Hg have units of nmol/L and $\mu g/m^3$, respectively. The values shown in parentheses represent the product of the standard error and the t-statistic and can be used to calculate the upper and lower 95th percentile confidence limits. The regression coefficient indicates that the regression captured only 23% of the total variability. As a

[2] The source of this difference is not known since the pattern of results on the reanalyzed regression was comparable to that shown as Figure 2 in Linstedt et al. (1979).

result this regression was not evaluated further to assess potential inter-individual variability.

Our reanalysis of the data from the second study yielded the following regression equation, which was consistent with that reported by the authors:

$$U\text{-}Hg = 3.52\ (\pm 5.77) \times Air\text{-}Hg + 114.62\ (\pm 138.74) \qquad r^2 = 0.12$$

where U-Hg and Air-Hg have units of nmol/L and $\mu g/m^3$, respectively. The values shown in parentheses represent the product of the standard error and the t-statistic and can be used to calculate the 95th percentile confidence limits. Since this regression coefficient was less than that observed in the first study by these authors, this regression also was not evaluated further to assess potential inter-individual variability as an individual study.

In summary, three of the studies presented in Table 1 provided paired results of the U-Hg and Air-Hg for individual subjects. Of these, only Mattiussi et al. (1982) was useful in estimating the inter-individual variability to Hg exposure. The calculated variability had an average value of 1.8, based on the ratio of the upper and lower 95th percentile confidence bounds generated using @RISK.

Combined Studies Evaluation

Tsuji et al. (2003) recently reviewed more than 20 studies that examined the relationship between U-Hg and Air-Hg, particularly air levels more relevant for environmental exposures (i.e., <50 $\mu g/m^3$). For the study to be included in their analysis it had to clearly meet at least four established criteria. Preferably, it met seven established criteria. The four basic criteria included:

> "1) studies must contain multiple paired airborne and urinary Hg concentration data that are representative of the same time period and location of exposure; 2) subjects of studies should have chronic exposure to airborne Hg (i.e., at least 6 months based on the time for Hg in urine to reach steady state with exposure to Hg vapour); 3) air measurements should be collected over most of a day [preferably averaged over several days to ameliorate high reported variation in day-to-day exposures of workers (Symanski et al., 2000)] and should be expressed as a time-weighted average (TWA); and 4) urine data should be expressed as an average of multiple spot samples per individual or as an average of urinary data from several individuals."

Studies included in the analysis were: Bell et al. (1973), Lindstedt et al. (1979a,b), Mattiussi et al. (1982), Muller et al. (1980), Nordhagen et al. (1994), Roels et al. (1987), Smith et al. (1970), Stopford et al. (1978) and Yamamura (1990). Tsuji et al. (2003) accounted for the variation in urinary Hg levels due to differences in hydration by selecting data that were normalized to a specific gravity of 1.024. In studies where correction for hydration was made by expressing Hg concentration as µg/gram of

creatinine, Tsuji et al. (2003) converted the concentrations to µg/L, assuming an average of 1g/L of creatinine in urine.

As part of their assessment, Tsuji et al. (2003) attempted to develop a composite regression derived from the selected studies. Although the slopes of the individual regressions were similar, the intercepts were different in many cases. Consequently, Tsuji et al. (2003) developed independent regressions for the different studies. A number of these regressions were developed using log-transformed Air-Hg and U-Hg data, which were not used in the original studies.

Tsuji et al. (2003) found a significant correlation between Hg in air and in urine, even for air concentrations between 10 and 50 µg/m^3 and reported a ratio between air and urine of 1:1 to 1:1.5 (intercepts around 4-5) for those studies that used personal air samplers and a ratio of 1:2 to 1:3 (intercepts around 6-13) for those studies that used static area air samplers. Furthermore, the authors reported that the lower intercepts derived from personal sampling data more accurately predict urinary Hg levels from air concentrations.

For the analysis, a composite regression was initially developed from the individual regressions generated by Tsuji et al. (2003) for the seven studies shown in Table 2. This approach assumes that the predictions based on the different studies at the same exposure concentration reflect the potential inter-individual and intra-individual variability. Although much of the analysis performed by Tsuji et al. (2003) was based on log-transformed Air-Hg and U-Hg data, the regression parameter values generated by these authors from the 7 studies were based on linear models using untransformed data (Table 2). Tsuji et al. (2003) regressions were used to estimate the U-Hg (as µg/L) based on eight Air-Hg concentrations (1, 2, 5, 10, 15, 20, 25, and 30 µg/m^3). This yielded the following composite regression, which is also shown in Figure 1a:

$$\text{U-Hg} = 1.22\ (\pm\ 0.65) \times \text{Air-Hg} + 23.42\ (\pm\ 10.97) \qquad r^2 = 0.21$$

The values shown in parentheses represent the product of the standard error and the t-statistic and can be used to calculate the 95th percentile confidence limits.

Table 2. Summary of Regression Equation Inputs Generated by Tsuji et al (2003) Based on Linear Models of Untransformed Data

Study	Intercept	Slope	r-value
Ehrenberg et al (1991)	8.77	1.24	0.88
Lindstedt et al (1979a), Study I	77.1	1.33	0.46
Lindstedt et al (1979b), Study II	22.9	0.7	0.34
Mattiussi et al (1982)	5.83	1.18	0.91
Nordhagen et al (1994)	32.01	0.97	0.69
Roels et al (1987)	9.75	1	0.82
Stopford et al (1978)	7.57	2.13	0.9

Review of Figure 1a shows that one regression appears to overestimate the U-Hg compared to the other studies causing the poor r^2-value. This regression corresponds to the U-Hg estimated from the first study by Linstedt et al. (1979a). When this regression is omitted the following composite regression was generated with an improved r^2-value (Figure 1b):

$$\text{U-Hg} = 1.20\ (\pm\ 0.27) \times \text{Air-Hg} + 14.47\ (\pm\ 4.64) \qquad r^2 = 0.62$$

This figure shows the 95th percentile confidence bounds (identified as "95% CI") and the 95th percentile prediction interval (identified as "95% PI").

Following the same approach as was taken with the Mattiussi et al. (1982) regression, the contribution of the bounding estimates on the slope and intercept of the composite regression was evaluated by using the mean and standard deviation values for the slope (0.14) and intercept (2.30) as inputs to @RISK. Additional inputs or assumptions included the following:

- a normal distribution was assumed for both the slope and intercept;
- the input Air-Hg concentrations were 1, 2, 5, 10, 15, 20, 25, and 30 µg/m^3 (i.e. the same as those used to generate the regression); and
- 10,000 iterations were used.

The ratio of the 97.5th percentile and 2.5th percentile from this analysis was used to estimate the potential inter-individual variability. This ratio ranged from 1.4 to 1.9 (mean: 1.6) across the eight test Air-Hg concentrations.

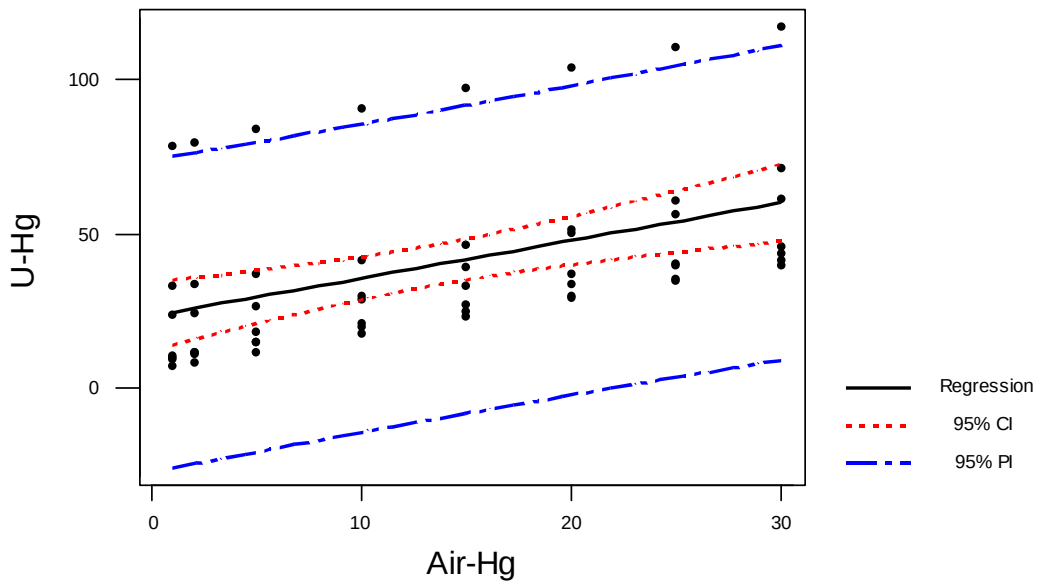

Figure 1a. Regression Generated by Combining Seven Studies Reported by Tsuji et al. (2003)

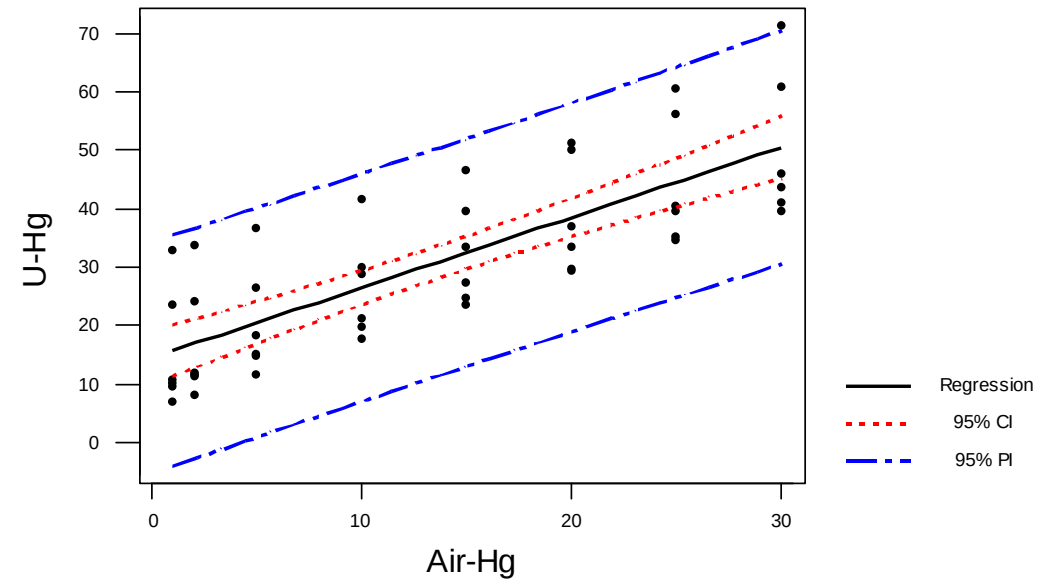

Figure 1b. Regression Generated by Combining Six Studies Reported by Tsuji et al. (2003)

Table 3 from Tsuji et al. (2003) lists the range and mean Air-Hg and U-Hg for 10 different studies. These data are reproduced in Table 3. The mean Air-Hg and U-Hg values from this table yielded the following regression:

$$\text{U-Hg} = 1.76\ (\pm\ 1.14) \times \text{Air-Hg} + 4.50\ (\pm\ 74.04) \qquad r^2 = 0.61$$

Although the r^2-value is much greater than observed in the previous regressions, the large confidence limits on the intercept result in negative values for the intercept which precludes the generation of representative bounding estimates using @RISK. Consequently, this regression was not evaluated further.

Based on regression analyses and @RISK simulations on individual studies and combined studies, the inter-individual variability was estimated to be approximately a factor of 2. This estimate was then corroborated using a pharmacokinetic approach that is described in the following section.

Table 3. Mean Air and Urine Hg Concentrations Reported by Tsuji et al (2003) from Ten Different Studies

Study	N	Air-Hg (ug/m^3)		U-Hg (ug/L)	
		Range	Mean	Range	Mean
Bell et al (1973)	4	73.1 - 151	107	70 - 154	112
Lindstedt et al (1979a) - Study I	13	34.3 - 111	63.3	76 - 307	162
Lindstedt et al (1979b) - Study II	15	14.7 - 43	23	3.4 - 65.4	39.1
Mattisussi et al (1982)	21	6.1 - 37.8	16.7	10.8 - 50.4	25.6
Muller et al (1980)	15	28.7 - 128	54.5	17.8 - 115	58
Nordhagen et al (1994)	34	13.4 - 191	61.9	31 - 251	92.3
Roels et al (1987)	10	15.7 - 89	40.9	13.4 - 100	51.5
Smith et al (1970)	18	3.5 - 272	102	68.2 - 773	255
Stopford et al (1978)	10	24 - 289	82	27.4 - 730	183
Yamamura (1990)	9	14 - 22	19.3	25 - 145	71.1

Assessment of Inter-Individual Variability Based on Pharmacokinetics of Hg in Humans

Another approach in estimating the potential inter-individual variability of Hg vapour is based on pharmacokinetic data. Our approach focused on studies that examined the pharmacokinetics of Hg vapour in humans exposed under different types of occupational settings (e.g., chloralkali plant, dental office) and studies that provided individual measurements or an appropriate summary parameter. Four studies met these criteria: Skare and Engqvist (1990); Barregård et al. (1992, 1996); and Ellingsen et al. (1993). In each case, elimination kinetics was reported. Two approaches were taken to estimate the inter-individual variability using the elimination rate constant (k_e):

- if the sample size was less than 5, then the ratio of the maximum and minimum k_e values was used; or

- if the sample size was 5 or greater, then the ratio of the upper and lower 95th percentile confidence bounds on the k_e values was used.

This distinction was made to minimize the inflation of the confidence bounds due to elevated t-values from small sample sizes. The results are summarized in Table 4 and are discussed below.

Table 4. Summary of Half-Times from Pharmacokinetic Studies of Hg Using Human Subjects

Ref	Ellingsen et al (1993)	Skare and Engqvist (1990)	Barregard et al (1992)		Barregard et al (1996)	
Model Type	Monophasic	Monophasic	Monophasic	Biphasic Slow Phase	Biphasic Fast Phase	Biphasic Slow Phase
Mean	72.4	44.8	49.8	119.8	7.8	90.4
SD	18.0	22.0	21.3	46.3	5.3	42.5
N	17	10	9	4	8	9
Min	68.3	22	26	57	2.3	34
Max	95.6	65	87	158	16	160
LCL	63.2	29.1	33.4	NC2	3.4	57.8
UCL	81.7	60.5	66.1	NC2	12.2	123.1
UCL/LCL Ratio	1.3	2.1	2.0	NC2	3.6	2.1
Max/Min Ratio	NC1	NC1	NC1	2.8	NC1	NC1

Notes:
NC1: Not calculated since there were sufficient number of samples to calculate UCL and LCL.
NC2: Not calculated since there were insufficient number of samples to calculate UCL and LCL.

Barregård et al. (1992) examined the elimination kinetics of Hg from nine individuals after short-term (20 to 45 hour) exposure to metallic Hg vapours at a chloralkali plant. The individuals were followed for 4 to 37 months. The authors normalized the U-Hg concentrations to creatinine content (reported as nmol Hg/mmol creatinine). Both one-compartment and two compartment models were fit to the data. As summarized in Table 4, the ratio of the confidence bounds on the half-times for the one-compartment model was 2.0 while the ratio of the maximum and minimum half-times for the two-compartment model (slow-phase) was 2.8. The authors did not calculate a two-compartment model fast phase due to paucity of data.

In a later study, Barregård et al. (1996) examined the elimination kinetics of Hg from 11 individuals exposed from 2 to 10 days to Hg vapours during maintenance activities at an unidentified industrial facility that produced zinc oxide and sulfuric acid. The individuals, some of whom exhibited neurological effects consistent with high Hg exposure, were followed for 1 to 11 months. Their U-Hg concentrations were normalized to creatinine content (reported as $\mu g/g_{cre}$) to adjust for variations in urinary flow rate. The U-Hg levels

ranged from 58 to 2,360 $\mu g/g_{cre}$ at the start of sampling (0 to 2 weeks from exposure cessation). One compartment and two compartment kinetic models were fit to the data by the authors. The two-compartment model consisted of a fast initial phase of elimination followed by a slow phase of elimination. Two individuals, who were tracked for the longest period, achieved U-Hg concentrations consistent with background (about 5 $\mu g/g_{cre}$; Tsuji et al., 2003) by the end of the study.

Our assessment focuses on the two-model compartment results (e.g., Barregård et al., 1996 data), since the two-compartment model provided the best fit to most of the kinetic losses by the 11 subjects. Table 4 summarizes the mean and confidence bounds of the half-times. Half-times could not be calculated for all subjects based on individual elimination behavior. Review of this table shows that the ratios of the confidence bounds on the k_e values ranged from 2.1 to 3.6.

Ellingsen et al. (1993) monitored the U-Hg concentrations in 17 former chloralkali workers after the cessation of their exposure. Individual exposure periods at the plant ranged from three days up to 36.5 years (mean: 6.7 years) and the follow-up period ranged from 155 to 366 days (mean: 254 days). The authors corrected the U-Hg concentrations for individual "baseline" Hg concentrations attributable to dental amalgams. A one-compartment model was fit to the data since the authors did not observe an initial fast phase in any of the individuals. The calculated half times are summarized in Table 4. The ratio of the confidence bounds on the Hg half-times of these 17 former chloralkali workers, after correcting for the contribution of existing amalgams for each individual, was less than 2.

Skare and Engqvist (1990) calculated the half-times of elimination of U-Hg in six dentists and four dental assistants. The elimination rates (as µg-Hg/day) were corrected for the number of amalgam surfaces in each individual using the following regression (from Skare et al., 1990):

$$\mu g\text{-Hg/day} = 0.6 + (0.07 \times N_t)$$

where N_t represents the number of amalgam surfaces. The excretion rates were calculated pre- and post-vacation. The vacation durations ranged from 36 to 56 days (mean: 38 days). The ratio of the confidence bounds on the Hg half-times of these 10 dental personnel, after correcting for the contribution of existing amalgams for each individual, was about 2 (Table 4).

Although not a pharmacokinetic study *per se*, Cherian et al. (1978) quantified the disposition of radio-labeled Hg (either ^{197}Hg or ^{203}Hg) in five human volunteers exposed for 14 to 28 minutes to Hg vapour. Due to the short-half life of ^{197}Hg (2.7 days; Weast, 1975), the five volunteers were monitored for a short period (about one week) using blood, urine or feces samples, and also with a whole-body counter. The observed variations in the individual body burdens were likely due to different inhalation rates and exposure durations. The authors adjusted for some of this variability by normalizing excretion loss based on the percent of retained dose. As summarized in Table 5, the

ratio of the confidence bounds on the percent of retained dose in the five healthy individuals after a short-term exposure to Hg was about 2.

In summary, half-times or elimination rate constants developed as part of pharmacokinetic studies suggest an inter-individual variability from 2 to 3 for Hg exposure.

Table 5. Summary of Retained Dose from Study be Cherian et al (1978)

	Excretion (% Retained Dose)		
	Urine	**Feces**	**Total**
Mean	2.40	9.24	11.64
SD	0.41	1.75	2.00
N	5	5	5
LCL	1.90	7.06	9.15
UCL	2.90	11.42	14.13
UCL/LCL Ratio	1.5	1.6	1.5

Assessment of Intra-Individual Variability of Hg Exposure and Response in Humans

The assessment of the potential intra-individual variability to Hg exposure in humans ideally requires the evaluation of data collected across different times for the same individual or groups of individuals. Unfortunately, most of the published studies do not include this level of detail. Two exceptions are studies by Bell Jr. et al. (1973) and Lindstedt et al. (1979a,b).

Bell Jr. et al. (1973) collected urine samples from four individuals that were performing different activities at a chlorine facility. A single sample was collected on Monday at the start of the work day, then the following Friday at three different times (start of the work day, prior to lunch break, and at the end of the work day). The U-Hg samples were normalized to a specific gravity of 1.024. Information on the Air-Hg concentrations was not provided by the authors. The key results from this study are summarized below:

- The ratios of the maximum and minimum U-Hg across the collection periods for each individual ranged from 1.4 to 3.3 (mean: 2.2).

- To estimate the change in U-Hg concentrations during the work week (i.e., exposure period), ratios of the U-Hg samples collected at the start of the work day on Friday and on Monday were calculated. These ratios were calculated for each individual and ranged from 1.1 to 3.3 (mean: 1.9). For all four individuals the Monday morning U-Hg concentrations were less than the Friday morning U-

Hg concentrations, reflecting exposure during the work week and minimal exposure over the weekend.

Too few individuals were available to use analysis of variance to discern either inter-individual or intra-individual variability.

Lindstedt et al. (1979a,b) provided the number of replicate urine samples per individual and the standard deviation of the mean U-Hg concentrations. Two sets of data were provided: the first summarized the U-Hg concentrations without normalizing to a specific gravity while the second data set presented U-Hg concentrations normalized to a specific gravity of 1.024. The key results are summarized below:

- The ratios of the upper and lower 95th confidence limits of the U-Hg concentrations (uncorrected for specific gravity) across the 13 individuals in the first dataset ranged from 1.3 to 2.3 (mean: 1.6).

- The ratios of the upper and lower 95th confidence limits of the U-Hg concentrations (corrected for specific gravity) across the 15 individuals in the second dataset ranged from 1.0 to 1.2 (mean: 1.1).

Variations in U-Hg related to sampling time and normalizing to specific gravity have also been reported in other studies (e.g., Piotrowski et al., 1975; Wallis and Barber, 1982). These results indicate that there needs to be consistency in the time of collection of the urine samples to minimize the variability in the U-Hg results.

These results suggest a potential intra-individual variability may be as large as 2, which is similar to the results obtained when other studies attempted to minimize the intra-individual variability.

Summary and Conclusions

Multiple lines of evidence support a total variability factor of approximately 2 in terms of the pharmacokinetics of Hg. Due to constraints in study designs and objectives, it is difficult to accurately quantify the contribution of inter- and intra-individual variability to the total potential variability in response (U-Hg concentration) to Hg vapour exposure. There are also other sources of uncertainty in this analysis. The supporting data are based primarily on healthy male subjects. As discussed in more detail in Section 4, there is evidence, albeit limited, to suggest a gender difference in uptake, distribution, and susceptibility to Hg vapour toxicity. Studies indicate that males metabolize and eliminate Hg more quickly than do females, and that after exposure to Hg tends to be distributed differently in males and females. While Hg appears to be distributed more quickly to the kidney and urine in males, it appears to be retained for a longer duration in females and thus be more available. In addition to any gender differences, one also needs to consider any pharmacokinetic differences that might exist among sensitive

populations, e.g., young children or chronically ill individuals when characterizing inter-individual uncertainty. Section 7 provides a final recommendation of the intraspecies uncertainty.

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