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The Aging Kidney and the Nephrotoxic Effects of Mercury

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Abstract

Owing to advances in modern medicine, life expectancies are lengthening and leading to an increase in the population of older individuals. The aging process leads to significant alterations in many organ systems, with the kidney being particularly susceptible to age-related changes. Within the kidney, aging leads to ultrastructural changes such as glomerular and tubular hypertrophy, glomerulosclerosis, and tubulointerstitial fibrosis, which may compromise renal plasma flow (RPF) and glomerular filtration rate (GFR). These alterations may reduce the functional reserve of the kidneys making them more susceptible to pathological events when challenged or stressed, such as following exposure to nephrotoxicants. An important and prevalent environmental toxicant that induces nephrotoxic effects is mercury (Hg). Since, exposure of normal kidneys to mercuric ions might induce glomerular and tubular injury, aged kidneys, which may not be functioning at full capacity, may be more sensitive to the effects of Hg than normal kidneys. Age-related renal changes and the effects of Hg in the kidney have been characterized separately. However, little is known regarding the influence of nephrotoxicants, such as Hg, on aged kidneys. The purpose of this review was to summarize known findings related to exposure of aged and diseased kidneys to the environmentally relevant nephrotoxicant, Hg.

Keywords

mercury; aging; kidney; glomerulosclerosis; heavy metals; chronic kidney disease

Introduction

In the past century, advances in modern medicine have significantly extended the life-expectancy of humans in developed and developing countries. According to the World Health Organization, the global life expectancy has risen from 64 years in 1990 to 72.1 years in 2013 (WHO 2016). In developed countries such as the United States, the average life expectancy has increased from approximately 47 years in 1900 to 79 years in 2011. Similar trends exist for other developed countries such as the United Kingdom, Canada, France, and Germany (WHO 2016). Elevation in life expectancy has led to a rise in the number of older

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Declaration of Interest

The authors report no conflicts of interest.

individuals. In the United States alone, the number of individuals over the age of 65 is projected to be 88.5 million by 2050 (USCB 2010). Globally, it is currently estimated that approximately 901 million individuals, i.e., 12% of the population, are over the age of 60. Because of lengthening life expectancies, this figure is expected to rise to 2 billion by 2050 (UN 2016). Older individuals make up a significant fraction of healthcare patients and thus, a thorough understanding of the impact of aging on organ systems, such as the renal/urinary system, is critical when managing the healthcare of these individuals.

Further, aging may enhance individual susceptibility to disease as well as increase one's risk of being affected adversely by exposure to environmental and/or occupational toxicants. Because of an increased life expectancy and elevated levels of pollution in the environment, it is likely that older individuals may be exposed more frequently and possibly to higher levels of toxic pollutants than individuals were decades ago. In particular, the kidney appears to be a major site of age-related changes and it may also be a target for heavy metals and other toxicants due to its role in filtration and excretion of these compounds. Given this, it is important that normal aging processes and the influence of potential toxicants on kidneys of older individuals are understood more comprehensively.

Aging and the Normal Kidneys

Numerous deleterious structural and physiological changes often occur in the kidneys as individuals age, especially after the seventh decade of life. These changes are likely the consequences of factors such as age-related hemodynamic changes, renal or non-renal disease, and/or life-long exposure to environmental and/or occupational toxicants. Interestingly, aged kidneys are capable of maintaining normal renal function and systemic homeostasis in healthy older individuals even though the normal aging process leads to significant deleterious structural and physiological consequences. The maintenance of normal renal function is at the cost of the renal functional reserve, which is the ability of the kidney to maintain glomerular filtration rate (GFR) when challenged. Once the functional reserve is depleted, kidneys have a reduced capacity to respond to challenges such as those associated with altered hemodynamics. In addition, the ability of the kidneys to eliminate circulating toxicants is most likely lower than normal. Because renal functional reserve may be significantly reduced in older individuals, the kidneys, and possibly other organs, of these individuals may be more susceptible to physiological, pathological, and toxicological challenges.

Molecular Changes within Renal Cells of Aged Kidneys

The aging process results in numerous complex and interrelated changes at the cellular and molecular levels. One such change is an inability to repair or replace injured cells. The mitotic index for renal epithelial cells is normally low, with proliferation occurring in approximately 1% of renal tubular cells (Humphreys et al. 2008). However, this % declines with age and thus, the ability of renal tubules to repair themselves may be reduced significantly in aged kidneys (Schmitt and Cantley 2008). Indeed, evidence from studies in kidneys of aged male C57Bl/6 mice (> 18 months) demonstrated that aging reduces the normal proliferative responses that follow an acute insult to renal tubular cells (Schmitt

2006; Berkenkamp et al. 2014). Analyses of kidneys from older human subjects (> 71 years) showed that renal levels of cytokines such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF) (Chou et al. 1997; Shurin et al. 2007; Hadem and Sharma 2016), which play roles in cell proliferation, decrease as humans age. The reduction in these cytokines may be an important factor in the inability of aged kidneys to initiate efficient cellular repair mechanisms. In addition, microarray analyses of DNA from kidneys of older humans suggested that certain genes involved in energy metabolism, and nucleotide, amino acid and/or protein turnover are down-regulated in aged kidneys (Melk et al. 2005). Further, a recent study showed that expression of the organic anion transporter 1 (OAT1) and VEGF was decreased in aged animals (Oliveira et al. 2016). In contrast, expression of select genes involved in immune and inflammatory processes was found to be enhanced in aged kidneys (Melk et al. 2005; Brink et al. 2009). For example, tumor necrosis factor (TNF)- α , C-reactive protein (CRP), NF- κ B, and interleukin (IL)-6, which are involved in the initiation of an inflammatory response, were expressed at greater levels in older humans (Bruunsgaard et al. 2001; Gerli et al. 2000; Mysliwska et al. 1999; Keller et al. 2007; O'Brown et al. 2015; Wiggins et al. 2010). Elevated expression of NF- κ B in kidneys of older individuals appears to be a particularly important regulator of the aging process in that it control cell-cycle exit and mediates age-related transcriptional changes (Helenius et al. 1996; Adler et al. 2007). In addition, it appears that the regulatory control of apoptotic processes is altered by the aging process in that the basal levels of apoptosis were found to be elevated in aged kidneys (Joaquin and Gollapudi 2001).

The aging process also appears to alter regulation of the cell cycle. Ding and colleagues (2001) examined senescent tubular epithelial cells and detected an elevation in the expression of transforming growth factor β -1 (TGF- β 1), which plays a role in cell cycle regulation. In addition, p21^{WAF1/CIP1} and p16^{INK4A}, which are thought to be involved in the regulation of cell growth, appear to be upregulated in senescent renal epithelial cells (Yang and Fogo 2010; Susnik et al. 2015; Berkenkamp et al. 2014). Increased levels of these proteins led to a dysregulation of the cell cycle and cell growth, which consequently resulted in defective cell proliferation and regeneration (Berkenkamp et al. 2014).

Aging has also been associated with alterations in DNA methylation and repair. In most tissues, DNA methylation increases early in life and falls in late adulthood (Jones et al. 2015). A general decrease in the stability and precision of DNA methylation occurs with age and leads to genomic and cellular instability, which contributes to cellular senescence (Pal and Tyler 2016).

Sirtuins have also been implicated as regulators of healthy aging in many organs, including the kidney. These proteins are Class III histone deacetylases that catalyze the deacetylation of proteins in a reaction that consumes NAD⁺ (Poulose and Raju 2015). Sirtuins are present in renal cells where they appear to protect against development of age-related diseases such renal interstitial fibrosis (Sebastian et al. 2012; Hao and Haase 2010; Ponnusamy et al. 2014). The sirtuin isoform, SIRT1 (silent information regulator-1), appears to promote healthy renal aging by playing a regulatory role in a number of cellular processes, such as gene silencing, lipid homeostasis, mitochondrial biogenesis and cellular respiration (Poulose and Raju 2015; Yuan et al. 2016). Indeed, decreases in the renal levels of SIRT1 protein

were detected in aged animals (Lim et al. 2012). In general, deactivation or downregulation of sirtuins appears to lead to dysregulation of a number of cellular processes, which in turn, may promote cell senescence and aging (Poulose and Raju 2015; Yuan et al. 2016; Yang and Fogo 2010).

Another mediator in the aging process is the anti-aging protein, Klotho. Klotho exists as a membrane protein, an intracellular protein, and as a soluble (secretable) protein (Kim et al. 2015a). Klotho is present in a number of organs, but its expression is particularly high in epithelial cells lining the proximal and distal tubules of the kidney (Hu et al. 2010; Li et al. 2004). The mechanisms by which Klotho slows the aging process have not been characterized completely. However, it is thought that the ability of Klotho to suppress reactive oxygen species (ROS)-derived oxidative stress, stimulate nitric oxide (NO) production, and maintain calcium and phosphate homeostasis in renal cells may have important anti-aging effects (Xu and Sun 2015; Saito et al. 1998). Interestingly, inflammation was found to reduce protein levels of Klotho, which may, subsequently, promote the aging process (Ohyama et al. 1998). In addition, hyperperfusion of glomeruli and resulting injury to the glomerular endothelium was also shown to reduce levels of Klotho and accelerate the aging process (Aizawa et al. 1998; Sugiura et al. 2012). Interestingly, studies in Klotho mutant mice demonstrated that development of age-related diseases such as stroke, arteriosclerosis, and osteoporosis was accelerated while overexpression of Klotho in mice appeared to slow the aging process (Masuda et al. 2005).

Injury to mitochondria appears to be an important factor in cellular senescence and aging. The mitochondrial free radical theory of aging, as proposed initially by Harman (1972; 1956) as described in Eirin et al (2016), suggests that generation of ROS from the mitochondrial respiratory chain increases with age, and consequently leads to oxidative damage within cells. Mitochondrial DNA appears to be a major target for mitochondrial-derived ROS. Injury to mitochondrial DNA impairs the function of the respiratory chain, which results in additional ROS formation and DNA injury. This cycle of events is thought to initiate other oxidative events that may lead to mitochondrial destabilization, cellular injury and cellular aging (Poulose and Raju 2014). These events may promote inflammation and enhanced deposition of extracellular matrix, which results in interstitial and parenchymal fibrosis and acute kidney injury (Guimaraes-Souza et al. 2015; Small et al. 2012; Akcay et al. 2009; Kinsey et al. 2008).

In recent years, a number of investigators started to identify the molecular basis of ROS-induced cellular injury. Data from several studies using aged mice indicate that aged animals display significant reductions in expression of various oxidative stress-related enzymes such as superoxide dismutase (SOD) 1, SOD2, catalase (CAT), and glutathione peroxidase (GPx) (Lim et al. 2012; Gomes et al. 2009; Cand and Verdeti 1989; Wang et al. 2014). These decreases eventually lead to a rise in the level of free radicals, which consequently results in cellular injury. In addition, microRNAs (miRNAs), which are small, non-coding regions of RNA, appear to be involved in the regulation of genes related to cellular metabolism, oxidative stress, and extracellular matrix degradation (Lapierre et al. 2015). Specifically, upregulation of miR-335 and miR-34a appears to diminish the expression of SOD2 and

thioredoxin reductase 2 (Txnrd2) (Bai et al. 2011). A reduction in the activities of these enzymes and others may lead to elevated oxidative stress, cellular injury, and cellular aging.

Structural Changes within Glomeruli of Aged Kidneys

Significant ultrastructural changes occur within the glomerulus as the result of the normal aging process. Indeed, several investigators reported that approximately 30–40% of all glomeruli become sclerotic by the eighth decade of life (Kaplan et al. 1975; Epstein 1996; Rodriguez-Puyol 1998; Kappel and Olsen 1980). Typical sclerotic glomeruli are characterized by a thickened glomerular basement membrane, expanded mesangial matrix, and shrinkage and occlusion of the glomerular capillaries (Figure 1) (Rodriguez-Puyol 1998; Zhou 2008; Lerma 2009; Thomas et al. 1998; Bridges et al. 2014; Denic et al. 2016). Although the pathogenesis of glomerulosclerosis is not completely understood, it is postulated to involve multiple factors, including alterations in blood flow, increased susceptibility to inflammatory cytokines, and damage to the glomerular filtration barrier (Figure 2) (Lopez-Novoa 2008; Wiggins et al. 2010; Silva 2005). A reduction in the total number of functioning nephrons appears to be an additional contributing factor in the development of glomerulosclerosis. As nephrons are lost, vascular and glomerular alterations occur in the remaining functional nephrons as an attempt to compensate for diminished total GFR (Lopez-Novoa 2008; Zatz and Fujihara 1994; Denic et al. 2016; Karam and Tuazon 2013). These changes lead to glomerular hypertrophy, hyperperfusion, and hyperfiltration, which increase single nephron GFR (SNGFR) and thus, predispose affected glomeruli to sclerotic changes (Lopez-Novoa 2008; Fogo 2000; Weinstein and Anderson 2010; Anderson and Brenner 1986). Indeed, a positive correlation between glomerular hypertrophy and development of glomerulosclerosis was demonstrated in aging mice (Ferder et al. 1994). In addition, proliferation of mesangial cells and expansion of mesangial matrix, both of which are often associated with glomerular hypertrophy, appears to precede and contribute to the development of glomerulosclerosis (Floege et al. 1992). Alternatively, age-related glomerulosclerosis may occur via immunologic mechanisms whereby formation of circulating or *in situ* immune complexes leads to glomerulonephritis (Silva 2005).

Interestingly, glomeruli in the outer cortex appear to be affected earlier and more severely by sclerotic changes than those in the juxtamedullary region (Rodriguez-Puyol 1998; Ljungqvist and Lagergren 1962; Choudhury 2004). As cortical glomeruli degenerate, glomerular capillaries atrophy, which leads to sclerosis. Interestingly, in juxtamedullary glomeruli, a direct channel is formed between afferent and efferent arterioles resulting in arterioles that do not communicate hemodynamically with a glomerulus (Lopez-Novoa 2008). In general, these aberrant glomeruli tend to be larger than cortical glomeruli; therefore, a significant reduction in the functionality of this population of glomeruli likely leads to significant decrease in whole-body GFR. An important marker of glomerular damage is proteinuria, which results from a disruption of the glomerular filtration barrier. Indeed, several studies suggested that injury to and dysfunction of podocytes, which are key components of the glomerular filtration barrier, may play a role in the pathogenesis of age-related glomerulosclerosis (Wiggins 2009; Camici et al. 2011; Wharram et al. 2005).

Structural Changes in Renal Tubules and Interstitium of Aged Kidneys

Age-related changes also occur in renal tubules and interstitium. These alterations include atrophy and degeneration, formation of diverticula, irregular thickening of the tubular basement membrane and tubulointerstitial fibrosis, which is associated with interstitial inflammation, fibroblast activation, and enhanced deposition of collagen (Thomas et al. 1998; Ding et al. 2001; Abrass et al. 1995; Zhou et al. 2008; Denic et al. 2016; Karam and Tuazon 2013). Macrophages and myofibroblasts, which are involved in collagen deposition, were identified in interstitial areas of fibrosis (Nakatsuji et al. 1998). The presence of myofibroblasts in these areas correlates with greater deposition of collagens (types I and III) (Nakatsuji et al. 1998) and non-collagenous proteins (Abrass et al. 1995) found in the interstitial space of fibrotic nephrons. This deposition is probably a primary cause of fibrosis and expansion of the interstitium. In addition, apoptosis of tubular and interstitial cells appears to be enhanced in fibrotic areas (Thomas et al. 1998). Apoptosis of these cell populations may be one reason for the observed decrease in volume, length, and number of tubular segments from fibrotic nephrons (Lindeman and Goldman 1986; Silva 2005; Zhou et al. 2008). As a consequence of these structural changes, alterations in tubular function may also occur. These alterations may include a diminished ability to concentrate/dilute urine (Rowe et al. 1976), maintain acid/base balance (Adler et al. 1968), and filter solutes (Macias-Nunez and Lopez-Novoa 2008; Zhou et al. 2008).

Physiologic Changes in the Aged Kidney

Since the aging kidney is subjected to considerable alterations in structure, it is not surprising to find that GFR also changes significantly as the kidney ages (Choudhury 2004; Zhou et al. 2008; Musso and Oreopoulos 2011; Rodriguez-Puyol 1998; Davies and Shock 1950; Lerma 2009). Beginning around 40 years of age, it is estimated that total GFR decreases by approximately 10% per decade of life (Baylis and Schmidt 1996; Davies and Shock 1950; Lerma 2009; Silva 2005; Weinstein and Anderson 2010). The rate of decline was found to rise after the age of 65 (Macias-Nunez and Lopez-Novoa 2008; Shock 1946; Davies and Shock 1950). The Baltimore Longitudinal Study of Aging, which collected data from patients aged 17 to 96, over a 23-year period, found that creatinine clearance (i.e., GFR) declined by 0.75 ml/min per year (Lindeman et al. 1985; Shock 1984). This decrease appears to be due to multiple factors including glomerulosclerosis, injury to and inadequate regeneration of podocytes, and an eventual reduction in the total number of functioning nephrons (Rule et al. 2011; Wharram et al. 2005; Hoshi et al. 2002). The overall findings of the Baltimore Longitudinal Study of Aging indicated that GFR fell steadily over time. However, of the 254 patients evaluated, 92 (36%) showed no significant reduction in GFR (Lindeman et al. 1985). Interestingly, individual variations in the expression of certain genes, such as those related to cell cycle regulation, may be linked to the tendency to develop age-related glomerular changes that lead to diminished GFR (Zheng et al. 2003; Melk et al. 2004; 2005; Zha et al. 2008). Thus, individual variations in gene expression may account for the lack of change in GFR observed in some patients. Despite the mixed findings of the Baltimore Longitudinal Study, there is overwhelming evidence to suggest that a decline in GFR is a normal consequence of aging (Glassock and Winearls 2009; Davies and Shock 1950; Epstein 1996; Silva 2005; Glassock and Rule 2016).

In addition to changes in GFR, aging also appears to affect renal blood flow (RBF) to the kidney (Choudhury 2004; Epstein 1996; Lerma 2009). Maximal RBF is reached around the third decade following which, RBF was found to decrease by approximately 10% per decade of life (Rodriguez-Puyol 1998). This fall appears to be related to alterations in vascular resistance in afferent and efferent arterioles rather than to changes in cardiac output (Naeije et al. 1993) or renal perfusion (Hollenberg et al. 1974). Because the decrease in total GFR is generally less than reduction in RBF, filtration fraction (FF) rises in most patients (Silva 2005; Epstein 1996; Choudhury 2004; Baylis and Schmidt 1996). It should be pointed out that although overall RBF falls, variable changes in blood flow occur at the level of the individual nephron. Within a single, hypertrophied nephron, RBF increases as a result of the hypertrophic changes that occur within that nephron (Fine 1992; Hayslett 1979). Elevation in RBF may lead to increased intraglomerular pressure, which may consequently result in glomerular injury.

Renal functional reserve (RFR) may also be altered in older individuals. Renal functional reserve has been defined as the ability of the kidney to increase its basal RBF and GFR by 20% or more after a stimulus, such as a protein load (Musso and Oreopoulos 2011; Bosch et al. 1986). Studies of RFR in older individuals yielded mixed results. While some investigations found that RFR is preserved to some extent in healthy individuals, aged 61–82 (Bohler et al. 1993; Fliser et al. 1993), Esposito and colleagues (2007) demonstrated that RFR is reduced or depleted in older individuals in order to accommodate for the age-related decline in renal function and as an attempt to preserve normal renal function. Musso et al. (2011) also found that RFR of older individuals remained intact, but its magnitude was lower than that in younger individuals. Similarly, *in vivo* studies using aged Sprague-Dawley rats provided evidence for an age-related decline in RFR (Uriu et al. 2000). In addition, the functional reserve of the kidneys appears to be decreased or absent in patients with diseases such as diabetes and hypertension (Raes et al. 2007; Zaletel et al. 2004; Gabbai 1995; Pecly et al. 2006).

Aging and Kidney Disease

There is an apparent association between aging and development of kidney disease. One can speculate that as the kidneys age, these organs lose their capacity to cope with certain challenges. Therefore, when an aged kidney is challenged, physiologically, pathologically or toxicologically, renal function may be affected. Indeed, an epidemiological study analyzing 437 cases of acute renal failure in Spain demonstrated that acute renal failure was 3.5-fold more prevalent in adults over the age of 70 than in younger adults (Pascual et al. 1990). Similarly, an analysis of data obtained from the Third National Health and Nutrition Examination Study (NHANES) in the United States noted that the incidence of chronic kidney disease (CKD) increases with age (Coresh et al. 2003; USRDS 2015). Coresh et al. (2003) noted that, even in the absence of other diseases such as hypertension and diabetes, approximately 11% of individuals over the age of 65 were diagnosed with moderate to severe renal failure. The progression of renal failure also appeared to occur more rapidly in aged than younger patients (Coresh et al. 2003; O'Hare et al. 2007). Ali and colleagues (2007) examined elderly patients with acute or chronic renal failure and suggested that older individuals are at greater risk of morbidity associated with their disease.

Comorbidities such as hypertension, cardiovascular disease, diabetes, and obesity are common in the elderly population (Table 1) and are considered to be significant risk-factors for the development of CKD (Abdelhafiz et al. 2010; Silva 2005; Anderson et al. 2009). In the United States, approximately 30% of the adult population is affected by hypertension (Yoon SS 2010; Keenan and Rosendorf 2011; Nwankwo et al. 2013), the incidence of which has been shown to increase with age (Nwankwo et al. 2013). Indeed, approximately 65% of adults over the age of 60 were diagnosed with hypertension (Keenan and Rosendorf 2011; Nwankwo et al. 2013), which has been associated with more rapid progression of CKD (Perry et al. 1995). A similar trend exists for diabetes, which affects approximately 29 million individuals in the United States (CDC 2014). Of individuals aged 65 and older, nearly 26% were diagnosed with diabetes (CDC 2014) and approximately 30% of these patients may develop CKD later in life (NKF 2016). The incidence of cardiovascular disease and obesity, which are also risk factors for CKD, is also greater in the older population (> 60 years) (Ogden et al. 2015; CDC 2014). The presence of diseases such as hypertension and/or diabetes in aging patients may enhance the normal age-related decline in renal function (Abdel-Kader and Palevsky 2009). Therefore, it is reasonable to suggest that older patients with superimposed diseases are more susceptible to development of CKD. It is also important to consider the rise in prescription drug use in older individuals. Not only does aging lead to a reduction in renal function, but it may also lead to a decrease in drug metabolism and elimination of drug metabolites (Jerkic et al. 2001; Rawlins et al. 1987; Kinirons and O'Mahony 2004; Hilmer et al. 2005). For example, non-steroidal anti-inflammatory drugs (NSAIDs) may be used frequently by older individuals. In fact, the use of these drugs by the aged and elderly population is estimated to be 3-fold higher than that of the younger population (Jerkic et al. 2001). In addition, the time required to metabolize and eliminate drugs was demonstrated to be greater in the elderly than in younger individuals (Cuny et al. 1979; Hilmer et al. 2005; Ruscin 2016). The altered handling of drugs may be due, in part, to age-related loss of renal function. Considering the elevated use and reduced elimination of certain drugs in older individuals, it is possible that utilization of these drugs may predispose individuals to renal injury and/or insufficiency.

Aging and Exposure to Mercury

Mercury is a Major Environmental Nephrotoxicant

Since toxic metals are abundant in the environment as well as in many occupational settings, human exposure to these metals is inadvertent and inevitable. Exposure of older individuals to toxic metals that are also nephrotoxicants may promote or enhance the progression of renal disease (Jarup et al. 1995; 1998; Kim et al. 2015b; Hellstrom et al. 2001; Moriguchi et al. 2005). Mercury (Hg) is a toxic metal that is of particular concern since certain forms are highly nephrotoxic while exposure to other forms may lead to significant neurotoxic effects. Mercury can exist in elemental (metallic), inorganic, and/or organic forms. Elemental mercury (Hg^0), which exists as a liquid at room temperature, has a low vapor pressure and thus, vaporizes readily to become Hg vapor. Inorganic Hg may be found as mercurous (Hg^{1+}) or mercuric (Hg^{2+}) ions, which are usually bound to chlorine, sulfur, or oxygen to form mercurous or mercuric salts. In the environment, inorganic Hg is usually found in the mercuric form. Organic forms of Hg include phenylmercury, dimethylmercury, and

monomethylmercury. Of these forms, methylmercury (MeHg) is the most frequently encountered in the environment. MeHg is formed primarily when inorganic mercuric ions are methylated by microorganisms present in soil and water (ATSDR 2008; Clarkson and Magos 2006; Rooney 2007; Zalups 2000).

Humans may be exposed to various forms of Hg through occupational and environmental settings, although exposure may also be due to the presence of dental amalgams or the use of certain medicinal products (ATSDR 2008; Clarkson and Magos 2006; Risher and De Rosa 2007; Zalups 2000). The most common route of human exposure, however, is via the ingestion of food, primarily fish, contaminated with MeHg (Nunes et al. 2014; 2014; Wolff et al. 2016; Lopez-Barrera and Barragan-Gonzalez, 2016). The flesh of large predatory fish, such as northern pike, swordfish, shark, and some species of tuna may contain high levels of CH_3Hg^+ and represents a major source of Hg exposure (Siedlikowski et al. 2016; Burger and Gochfeld 2011). Upon ingestion, MeHg is absorbed readily by the gastrointestinal tract (Vazquez et al. 2013; 2014) following which, mercuric ions enter systemic circulation and are delivered to target organs.

Renal Handling of Mercury

Inorganic and organic forms of Hg accumulate readily in the kidney. Although the kidney is the primary site of accumulation and toxicity of inorganic forms of Hg, exposure to organic Hg (e.g., MeHg) may also lead to serious adverse effects in the kidney (Murphy et al. 1979; Rowens et al. 1991; Samuels et al. 1982; Yasutake et al. 1989). Within the kidney, the proximal tubule is the primary site of uptake and accumulation of mercuric species (Zalups 2000). It is important to note that following exposure to MeHg, a fraction of the absorbed CH_3Hg^+ is oxidized within tissues and cells to form Hg^{2+} (Gage 1964; Norseth and Clarkson 1970a; 1970b; Omata et al. 1980). It should also be noted that within biological systems, mercurous, mercuric, or methylmercuric ions do not exist as inorganic salts, or in an unbound, “free” ionic state (Hughes 1957). Alternatively, mercuric ions are bound to one or more thiol-containing biomolecules, such as GSH, cysteine (Cys), homocysteine (Hcy), *N*-acetylcysteine (NAC), or albumin. Hg^{2+} binds to thiol-containing molecules in a linear II, coordinate covalent manner whereas MeHg forms linear I, coordinate covalent complexes with thiol-containing molecules (Figure 3) (Fuhr and Rabenstein 1973; Rubino et al. 2004). In addition, Hg may also bind to selenium (Se). Several studies in humans showed that administration of Se to individuals exposed to Hg reduces the overall intoxication induced by Hg (Bjorklund 2015; Chen et al. 2006). It is not clear if Hg-Se complexes are transportable forms of Hg. It is interesting to note that the binding affinity of Hg is greater for Se than for thiols (Sugiura et al. 1978); however, the concentration of Se in blood is approximately 11 $\mu\text{mol/L}$ (Kucharzewski et al. 2002) while the concentration of Cys and GSH in blood is approximately 275 and 850 $\mu\text{mol/L}$, respectively (Michelet et al. 1995; El-Khairi et al. 2001). Since the normal blood concentrations of Cys and GSH are significantly greater than that of Se, it appears that circulating Hg is more likely to be bound to Cys and/or GSH than to Se.

Inorganic Hg accumulates rapidly in renal tissue with as much as 50% of a nontoxic dose present in the kidneys within a few hr after exposure (Zalups 1993). The majority of

mercuric ions accumulate in the epithelial cells lining the proximal tubule (Zalups 2000). Mercuric ions appear to be taken into proximal tubular cells via transport mechanisms present on the luminal and basolateral membranes (Cannon et al. 2000; 2001; Zalups 1998; Zalups and Lash 1997; Zalups and Minor 1995). The primary species of Hg^{2+} that is transported into cells at the luminal membrane appears to be a Cys-S-conjugate (Cys-S-Hg-S-Cys) of Hg^{2+} (Zalups and Barfuss 1995; 1996; 1998). Subsequent studies in isolated perfused tubules implicated amino acid transporters in the luminal uptake of thiol-S-conjugates of Hg^{2+} by proximal tubular cells (Cannon et al. 2000; 2001). Cys-S-Hg-S-Cys is similar in size and shape to the amino acid cystine (Figure 3), and thus, it was suggested that this mercuric conjugate may utilize a cystine transporter to gain access to the intracellular compartment of proximal tubular cells. Studies using Madin-Darby Canine Kidney (MDCK) cells stably transfected with the sodium-independent cystine transporter, System $\text{b}^{0,+}$, provide evidence implicating this carrier in the uptake of Cys-S-Hg-S-Cys from the tubular lumen into proximal tubular cells (Figure 4) (Bridges et al. 2004). Similar studies reported that the Hcy-S-conjugate of Hg^{2+} (Hcy-S-Hg-S-Hcy) is also transported by System $\text{b}^{0,+}$ (Bridges and Zalups 2004). As of yet, a sodium-dependent transport mechanism has not been identified for the luminal uptake of Cys-S-Hg-S-Cys and/or Hcy-S-Hg-S-Hcy into proximal tubular cells. In contrast, evidence from studies using *Xenopus laevis* oocytes indicates that Cys-S-conjugates of MeHg (Cys-S-MeHg), which are similar in shape to methionine (Figure 3) are substrates of the sodium-dependent amino acid carrier, System $\text{B}^{0,+}$ (Bridges and Zalups 2006). Currently, there are no apparent data supporting a role for System $\text{B}^{0,+}$ in the uptake of Cys-S-Hg-S-Cys or Hcy-S-Hg-S-Hcy (Bridges and Zalups 2006).

Approximately 40–60% of the Hg^{2+} that accumulates in proximal tubular cells appears to be taken up at the basolateral plasma membrane (Zalups and Barfuss 1995; 1998a; 1998b; Zalups 1995; 1998a; 1998b; Zalups and Minor 1995). The organic anion transporters (OAT) 1 and 3 are localized in the basolateral plasma membrane of proximal tubular epithelial cells (Kojima et al. 2002; Motohashi et al. 2002) and appear to be involved in the uptake of Cys-S-Hg-S-Cys, NAC-S-Hg-S-NAC, and Hcy-S-Hg-S-Hcy at the basolateral membrane of proximal tubular cells (Figure 4) (Zalups 1995; 1998a; 1998b; Zalups and Barfuss 1995; 1998a; 1998b; Zalups and Lash 1997; Aslamkhan et al. 2003; Zalups and Ahmad 2004; Zalups et al. 2004). Studies using cultured MDCK cells stably transfected with OAT1 indicate that mercuric conjugates of Cys, Hcy, and NAC (NAC-S-Hg-S-NAC) are all substrates of this carrier (Aslamkhan et al. 2003; Koh et al. 2002; Zalups and Ahmad 2004; Zalups et al. 2004). In addition, Cys-S-Hg-S-Cys also appears to be a transportable substrate of OAT3 (Aslamkhan et al. 2003). OAT1 was also found to mediate the basolateral uptake of MeHg, as a conjugate of Cys, NAC, or Hcy (Zalups and Ahmad 2005a; 2005b; 2005c). Interestingly, single nucleotide polymorphisms (SNP) in OAT1 and OAT3 have been associated with enhanced urinary excretion of Hg in certain populations (Engstrom et al. 2013). It should be noted that other studies suggest that SNP in OAT1 and OAT3 may not occur frequently enough in a population to significantly alter the renal handling of substrates by a large fraction of the population (Fujita et al. 2005; Xu et al. 2005).

Once mercuric ions enter the intracellular compartment of cells, they form strong bonds with protein and non-protein thiol-containing biomolecules. In particular, mercuric ions have a

strong affinity for intracellular metallothionein (MT) (Cherian and Clarkson 1976; Zalups and Koropatnick 2000). Exposure of animals to various forms of Hg increases intracellular levels of MT (Wisniewska et al. 1970; Piotrowski et al. 1974; Planas-Bohne et al. 1985). MT binds to mercuric ions within the cells and forms a stable complex that appears to reduce the intoxication produced by mercuric ions (Sato et al. 1997). This complex is also less likely to be transported out of cells leading to retention of mercuric ions within cells (Planas-Bohne et al. 1985; Zalups et al. 1993; 1995).

Mercuric ions also have a strong affinity for GSH (Fuhr and Rabenstein 1973) and may bind to GSH, both intracellularly and extracellularly. The concentration of GSH in renal tubular cells is in the mM range (Brehe et al. 1976), which makes GSH well-suited for binding to and neutralizing intracellular mercuric ions. Indeed, exposure of mice to HgCl_2 lowered renal levels of intracellular GSH (Bridges et al. 2013), suggest that GSH is utilized to counteract the oxidative effects of Hg^{2+} . In addition, the mRNA expression of glutamate-cysteine ligase (GCL), the rate-limiting enzyme in the synthesis of GSH, was found to be elevated following exposure to HgCl_2 (Bridges et al. 2013; Oliveira et al. 2016). This increased expression is likely an attempt to synthesize additional GSH in order to counteract the oxidative stress induced by exposure to Hg^{2+} . Although the binding of mercuric ions to intracellular biomolecules, such as GSH, is important to diminish the possibility of Hg-induced intoxication within the cell, this binding may also contribute to retention of mercuric ions within cells in that these GSH *S*-conjugates of Hg^{2+} may not be transported easily and/or readily out of cells.

In order to efficiently remove mercuric ions from within renal epithelial cells, metal complexing agents, such as 2,3-bis(sulfanyl)propane-1-sulfonic acid (formally known as 2,3-dimercaptopropane-1-sulfonic acid; DMPS) (Ruprecht 2008) or 2,3-dimercaptosuccinic acid (DMSA) (Aposhian 1983; Aposhian et al. 1992; 1995; Planas-Bohne 1981; Ruprecht 2008; Zalups 1993) are required. Several investigators demonstrated that DMPS and DMSA gain access to proximal tubular cells via OAT1, OAT3 and/or the sodium-dependent dicarboxylate transporter (NaC2) in the basolateral plasma membrane (Rodiger et al. 2010; Bahn et al. 2002; Burckhardt et al. 2002; Islinger et al. 2001). Once inside the cell, it is postulated that DMPS and DMSA (in their reduced forms) bind to mercuric ions to form DMPS or DMSA *S*-conjugates of Hg^{2+} or CH_3Hg^+ . These complexes appear to be secreted into the tubular lumen for eventual excretion in the urine (Aposhian 1983; Aposhian et al. 1992). Early studies examining the tubular secretion of thiol *S*-conjugates of CH_3Hg^+ implicated the multidrug resistance-associated protein 2 (Mrp2) in the export of NAC-*S*-conjugates of MeHg from proximal tubular cells (Aremu et al. 2008; Madejczyk et al. 2007). Similarly, studies utilizing TR^- (Mrp2-deficient) rats showed that Mrp2 is involved in the DMPS- and DMSA-mediated extraction of Hg^{2+} from proximal tubular cells (Bridges et al. 2008a; 2008b). In addition, *in vitro* studies utilizing inside-out, brush-border membrane vesicles prepared from *Sf9* cells transfected with human MRP2 provided direct evidence indicating that DMPS- and DMSA-*S*-conjugates of Hg^{2+} are transportable substrates of MRP2 (Bridges et al. 2008a; 2008b). MRP2 polymorphisms were also identified in certain populations and appear to enhance the urinary excretion of Hg in these populations (Engstrom et al. 2013). Ballatori (2002) proposed that GSH-*S*-conjugates of Hg^{2+} or CH_3Hg

⁺ may be transportable substrates of MRP2; however, at present, there are no apparent data to support this theory.

In addition to MRP2, the breast cancer resistance protein (BCRP) may play a role in proximal tubular export of mercuric ions. Studies using Bcrp knockout rats (*Bcrp*^{-/-}) noted that mercuric ions are retained within target organs such as kidney and liver in the absence of Bcrp (Bridges et al. 2015). These data suggest that Bcrp may play a role in the export of mercuric species from within renal tubular cells. Additional studies using inside-out membrane vesicles from *Sf9* cells overexpressing human BCRP provide direct evidence showing that DMPS *S*-conjugates of Hg⁺² are transportable substrates of BCRP (Bridges et al. 2015). Further *in vivo* studies are needed to fully characterize the role of BCRP in the transport of various thiol *S*-conjugates of Hg²⁺.

Renal Effects of Mercury Exposure

Exposure to all forms of Hg might lead to nephrotoxic effects (Murphy et al. 1979; Rowens et al. 1991; Samuels et al. 1982; Yasutake et al. 1989). In fact, numerous epidemiological studies reported evidence of renal injury following acute and chronic exposure to various forms of Hg (Ha et al. 2016; Pollack et al. 2015). However, the most severe nephropathy is induced following exposure to Hg²⁺. *In vitro* studies indicate that this nephropathy initially affects the *pars recta* of the proximal tubule, located in the inner cortex and outer stripe of the outer medulla, suggesting that this section of the nephron is the most sensitive to the toxic effects of Hg (Zalups 2000; Bridges et al. 2013; Zalups et al. 2014; Zalups and Diamond 1987). Exposure to moderate or high doses of HgCl₂ results in cellular necrosis along the *pars recta*, *pars convoluta* and distal segments of the nephron (McDowell et al. 1976; Zalme et al. 1976; Zalups et al. 2014). Under these conditions, cellular injury along the *pars recta* is rapid and signs of injury such as swelling of mitochondrial matrices and the presence of pyknotic nuclei may be detected via electron microscopy in as little as 3 hr (Rodin and Crowson 1962; Gritzka and Trump 1968). After 6 hr, cells begin to lose microvilli, mitochondrial swelling worsens and the endoplasmic reticulum becomes dilated (McDowell et al. 1976; Gritzka and Trump 1968). The activities of selected enzymes including alkaline phosphatase (AP), succinic dehydrogenase, arginase II in proximal tubular cells also appear to be diminished (Zalme et al. 1976; Kanda et al. 2008). Twelve hr after exposure to HgCl₂, electron microscopic analyses of *pars recta* segments revealed rupture of the plasma membrane, loss of microvilli, decreased contact with the basement membrane, and loss of cell shape (Gritzka and Trump 1968). After 24 hr, cellular fragments may be identified in the tubular lumen, junctional complexes between cells are absent, and nuclear structure is compromised (Gritzka and Trump 1968; Rodin and Crowson 1962; Zalme et al. 1976). When the plasma membrane of tubular epithelial cells is compromised, numerous brush-border and intracellular enzymes, such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), AP, γ -glutamyltransferase (γ -GT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glutathione peroxidase (GPx) were detected in urine (Zalups 1988a; 2000; Gotelli et al. 1985; Price 1982; Planas-Bohne 1981; Zalups and Diamond 1987; Prozialeck and Edwards 2010; Roels et al. 1999; Yasutake et al. 1997). Exposure of rats to nephrotoxic doses of Hg²⁺ was found to enhance renal expression of Kim-1 and Ngal

(Bridges et al. 2014). As Hg-induced renal injury progresses, there is also a simultaneous rise in urinary excretion of mercuric ions (Clarkson and Magos 1967; Magos and Stoytchev 1969; Trojanowska et al. 1971).

Accumulation of Hg within proximal tubular cells induces oxidative stress and exerts significant effects on enzymes that are responsible for reducing oxidative stress and managing detoxification within cells (Joshi et al. 2014a; 2014b; Stacchiotti et al. 2009). In a study of healthy male industrial workers in Saudi Arabia, chronic exposure to Hg was found to decrease renal expression of proteins involved in detoxification and the reduction of oxidative stress such as NAD(P)H:quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), alpha-glutathione S-transferase (GSTA1), MT-1, and heat shock protein 70 (HSP70) (Al Bakheet et al. 2013). Reductions in these protective mechanisms may further enhance the susceptibility of cells to intoxication and injury by toxicants such as Hg. Similarly, when healthy adult rats were exposed chronically to HgCl₂, renal levels of thiobarbituric acid reactive substances (TBARS) and GPx were found to be elevated, suggesting that Hg induces intracellular oxidative stress in renal epithelial cells (Agrawal et al. 2014). In the same study, levels of SOD, CAT, GSH, and glutathione disulfide (GSSG) were reported to be lowered suggesting that these enzymes were depleted in the process of counteracting the oxidative effects of Hg (Agrawal et al. 2014). In contrast, acute exposure of healthy rats to HgCl₂ led to an rise in enzymes such as AP and LDH (Joshi et al. 2014b), suggesting that the initial exposure to Hg leads to an early increase in enzyme levels, which may become depleted eventually if exposure to Hg becomes chronic. Exposure of renal cells to various species of Hg and subsequent induction of intracellular oxidative stress may also initiate mitochondrial injury and dysfunction, which results in a reduction in overall cell viability (Lund et al. 1993; Shenker et al. 1998; Carranza-Rosales et al. 2005; Carocci et al. 2014). Since many of the injurious cellular effects of Hg exposure are similar to those induced by aging, one should consider that exposure of aged kidneys to Hg may lead to effects that are synergistic, producing enhanced intoxication of proximal tubular cells.

Exposure to mercuric species may also result in pathological changes in glomeruli, such as membranous glomerulonephritis, which is characterized by a thickened glomerular basement membrane and proliferation of mesangial cells. Tubulointerstitial injury and fibrosis, granular degeneration of epithelial cells and infiltration of immune cells also occurs (Li et al. 2010; Zalups et al. 2014). Rats exposed to a non-nephrotoxic dose of HgCl₂ for 21 weeks developed significant tubular, interstitial and glomerular lesions (Hall et al. 1986), even though there were no significant differences in the measurable parameters of renal function such as plasma urea nitrogen, plasma creatinine, and protein excretion. Similarly, exposure of rats to MeHg for two years led to fibrotic changes in a fraction of glomeruli (Eto et al. 1997). In addition, deposits of IgG, IgM and C3 were detected along the glomerular basal lamina (Eto et al. 1997), which is characteristic of an immunological glomerulopathy (Druet et al. 1978; Bigazzi 1992; 1988; Zalups 2000). Glomerular changes such as fibrosis and thickening of the glomerular basal lamina often result in reductions in GFR. Therefore, it is not surprising that following exposure to Hg²⁺, decrease in GFR was observed (McDowell et al. 1976; Vanholder et al. 1982).

Based on these studies, it is apparent that acute and chronic exposure to mercuric compounds produces numerous, deleterious effects in the kidneys. Given that older individuals may have reduced functional renal mass due to glomerulosclerosis, tubular atrophy and interstitial fibrosis and GFR, it is possible that exposure of these individuals to mercuric compounds may be even more detrimental to the health of the patient. Unfortunately, few studies examined the link between age, exposure to mercuric compounds, and patient health.

Aging and the Effects of Mercury Exposure on the Kidney

Older individuals make up a significant percentage of the population, and exposure to mercuric compounds appears to be increasing, yet little is known regarding the relationship between aging kidneys and effects of Hg exposure on kidneys. Recent epidemiological studies in human populations indicate that the renal burden of Hg increases with age (Habiba et al. 2016; Song et al. 2016; Carneiro et al. 2014). Similarly, studies measuring bioaccumulation in wild roe deer from Spain and free-range European hares from Serbia also showed that the renal burden of heavy metals such as Hg increases as animals age (Petrovic et al. 2014; Hermoso de Mendoza Garcia et al. 2011). Recent *in vivo* studies utilizing two- and 20-month-old Wistar rats, demonstrated that the overall accumulation of Hg²⁺ was greater in kidneys of older than younger rats (Bridges et al. 2014; Oliveira et al. 2016). Similarly, Kostial et al (1978) compared the distribution of Hg²⁺ in 2-week-old to 21-week-old rats and found that renal accumulation of Hg²⁺ was higher in kidneys of older rats (Kostial et al. 1978). Interestingly, chronic exposure to MeHg was found to correlate with development of Type II diabetes (Schumacher and Abbott 2016) and hypertension (Houston 2011; Rajaei et al. 2015), which are considered to be significant risk factors of CKD (Ginsberg et al. 2014). Therefore, exposure to Hg may contribute to the development of CKD or it may enhance the progression of the disease. Indeed, a recent study of residents living near the Chatian Hg mine in southwestern China reported that older (> 60 years) individuals had higher blood Hg and serum creatinine levels (indicative of lower GFR) than adults (18 – 60 years) and children (< 18 years) in the same area (Li et al. 2013). Data suggest that older individuals who are exposed to Hg are more likely to experience renal insufficiency or CKD than older individuals who are not exposed to Hg. However, it is not clear if the increased blood Hg and creatinine levels are due simply to the age of the individuals or if there is a valid correlation between renal function and exposure to Hg. Alternatively, exposure to Hg may enhance progression or exacerbate symptoms of CKD in current patients. Because many patients in the early stages of CKD are asymptomatic (CDC 2012), a diagnosis is often not made until renal function has been compromised significantly and GFR is well below the normal range. During this period, patients may continue to be exposed to nephrotoxics including Hg. Such exposure may enhance morbidity and mortality as these patients may be more sensitive to the adverse effects of Hg. While an association between age, exposure to Hg, and CKD has not been established with certainty, there are a number of studies showing that exposure to nephrotoxic metals, such as lead (Pb), cadmium (Cd) and cisplatin, exacerbate renal insufficiency in older individuals (Ferraro et al. 2010; Noonan et al. 2002; Roels et al. 1991; Sommar et al. 2013; Kim et al. 2015b; Wen et al. 2015). Since exposure to Cd or Pb were found to exert adverse effects on renal

function of older individuals, it may be postulated that exposure of these individuals to Hg may also exacerbate renal disease.

Although, there are few human studies linking exposure of Hg to an enhanced risk of renal injury in older individuals, there are several reports using rat models that link exposure to Hg with reduced renal function. In aged kidneys, the total number of functioning nephrons has decreased significantly, which is similar to the renal mass of a uninephrectomized rat. Although the uninephrectomized rat model does not precisely mimic changes that occur in an aging kidney, there are similarities between the two systems. In each, a significant number of nephrons are lost and remaining nephrons need to undergo a compensatory, hypertrophic phase in order to maintain normal fluid and electrolyte homeostasis (Fine and Norman 1989; Fine 1992; Hayslett 1979). Hyperperfusion and hyperfiltration appear to occur in hypertrophied nephrons and may result in these nephrons being exposed to higher levels of nephrotoxics such as Hg. This increased exposure may enhance susceptibility of these nephrons to the deleterious effects of Hg or other nephrotoxics (Houser and Berndt 1986; 1988; Ramos-Frendo et al. 1979; Zalups 1991, 1997; Zalups et al. 1987;1992; Zalups and Diamond 1987) .

Several studies utilizing uninephrectomized rats support the idea that hypertrophied nephrons are more sensitive to the adverse effects of Hg. Ramos-Frendo and colleagues (1979) exposed uninephrectomized and sham rats to a nephrotoxic dose of HgCl_2 and found that development of Hg-induced renal failure was more pronounced in uninephrectomized animals than in shams. Similarly, Houser and Berndt (1986) exposed uninephrectomized and sham rats to a nephrotoxic dose of HgCl_2 , following which they assessed renal susceptibility to mercuric ions. Exposure to HgCl_2 induced glomerular and tubular dysfunction, which appeared to be more severe in uninephrectomized rats than in sham rats (Houser and Berndt 1986) . In a separate, more detailed study using uninephrectomized and sham Sprague-Dawley rats exposed to a nephrotoxic dose of HgCl_2 , it was discovered that mercuric ions were redistributed within the kidney following uninephrectomy (Houser and Berndt 1988). The concentration of mercuric ions was greater in renal cortex and outer stripe of the outer medulla in uninephrectomized rats than in shams. Not surprisingly, the urinary excretion of mercuric ions (per kidney) was greater in uninephrectomized rats than in shams (Houser and Berndt 1986; 1988). Similarly, Zalups and Diamond (1987) treated uninephrectomized and sham Long Evans hooded rats to nephrotoxic doses of HgCl_2 and noted that Hg-induced proximal tubular necrosis was more extensive in uninephrectomized than sham animals. In addition, urinary excretion of cellular enzymes and plasma proteins, including LDH, γ -glutamyltransferase and albumin, was greater in uninephrectomized than sham animals (Zalups 1997; Zalups and Diamond 1987). Collectively, the results of these studies indicate that kidneys of animals with reduced renal mass are more susceptible to adverse effects of Hg^{2+} . Similarly, it might be postulated that elderly and aged individuals who display reduced renal function due to normal aging processes and/or superimposed disease processes may be more susceptible to renal injury following exposure to a nephrotoxicant such as Hg.

Summary

The aging process in the kidneys was studied and characterized comprehensively. It is well-known that glomerulosclerosis leads to decreases in GFR and RBF. However, there is little information regarding the response of aged kidneys to environmental toxicants such as Hg. Because of the prevalence of Hg in the environment, human exposure is inadvertent and nearly unavoidable. Further, it is well-known that acute and chronic exposures to toxic metals may be detrimental to kidneys of normal adults, thus it may be postulated that exposure of individuals with CKD to these metals may result in additional reductions in renal function. Individuals with compromised renal function, either from aging, disease or a combination of aging and disease, may be particularly susceptible to nephrotoxicants. The potential association between aging and susceptibility to nephrotoxicants is supported by only a few studies. However, the available data appear to show an association between exposure to Hg and an increase in incidence and severity of renal disease. It is important to note that early signs of renal dysfunction often go unnoticed (CDC 2012), thus, individuals with reduced renal function are often unaware that they may be at risk during the early stages of disease. If exposure to nephrotoxicants occurs during this early period, this may be especially detrimental to these individuals. Therefore, a thorough and complete understanding of the manner in which nephrotoxicants are handled by aging kidneys is of utmost importance. Because of the paucity of data available on this topic, additional studies are clearly necessary.

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Figure 1. Age-related glomerulosclerosis and tubular necrosis in rat kidney.

Images shown are representative sections of kidneys from two-month-old (A & B) or 20-month-old (C & D) rats stained with hematoxylin and eosin (H & E). Panel A shows a glomerulus (arrow) within the renal cortex of young rats that displays normal glomerular morphology. Panel B shows normal proximal tubules (PT) within the outer stripe of the outer medulla (OSOM) of young rats. Panel C shows the renal cortex of older rats wherein glomeruli were swollen with thickened basement membranes (arrows) and capsules (arrowheads). Panel D shows proximal tubules (arrowheads) within the OSOM of older rats. Tubules were swollen with numerous cytoplasmic vacuoles and protein deposits (*) (200x).

Figure 2. Possible pathogenesis of age-related glomerulosclerosis.

Numerous factors, such as molecular and cellular changes and alterations in the hemodynamics and structure of the glomerulus may contribute to age-related glomerulosclerosis. These alterations may lead to glomerular hypertrophy followed by hyperperfusion and hyperfiltration of affected glomeruli. As a result of these hypertrophic changes, the single nephron glomerular filtration rate often increases, leading to glomerular injury, glomerulosclerosis, and renal insufficiency.

Figure 3. Similarities between mercuric species and amino acids.

The binding of cysteine (Cys) to inorganic mercury (Hg^{2+}) forms a linear II coordinate covalent complex (Cys-S-Hg-S-Cys) while binding of Cys to methylmercury (CH_3Hg^+) forms a linear I coordinate covalent complex (Cys-S-CH₃Hg). Cys-S-Hg-S-Cys is similar in shape and size to the amino acid, cystine while Cys-S-CH₃Hg is similar to the amino acid, methionine.

Figure 4. Schematic representation of the transport and toxicity of mercury in proximal tubular cells.

Inorganic (Hg^{2+}) and organic (CH_3Hg^+) forms of mercury enter proximal tubular cells as conjugates of thiols (cysteine, Cys; homocysteine, Hcy; N-acetylcysteine, NAC) at the luminal membrane via amino acid transporters and at the basolateral membrane via organic anion transporters (OAT) 1 and 3. OAT1 and 3 are driven by the circular movement of α -ketoglutarate (α -kg), which enters the cell via the Na^+ -dicarboxylate transporter (NaC3). Once inside the cell, mercuric conjugates may lead to changes in DNA methylation and repair, inflammation, mitochondrial injury, and oxidative stress. These cellular changes may also be caused by the aging process. Exposure of aged individuals to mercuric compounds may enhance the susceptibility of cells to injury because of the synergistic effects of age and mercury on the cells.

Table 1

Estimated number of older adults in the United States affected by chronic kidney disease (CKD) and its comorbidities.

	Hypertension > 60 years	Type II Diabetes > 65 years	Obesity > 60 years	Cardiovascular Disease		CKD >60 years
				65–74 years	> 75 years	
U. S. Adults	65.0 % ¹	25.9 % ²	37.0 % ³	24.6 % ⁴	35.0 % ⁴	33.2 % ⁵