Published in final edited form as:

J Toxicol Environ Health B Crit Rev. 2010 ; 13(5): 385–410. doi:10.1080/10937401003673750.

TRANSPORT OF INORGANIC MERCURY AND METHYLMERCURY IN TARGET TISSUES AND ORGANS

Christy C. Bridges, Rudolfs K. Zalups

Mercer University School of Medicine, Division of Basic Medical Sciences, Macon, Georgia, USA

Abstract

Owing to the prevalence of mercury in the environment, the risk of human exposure to this toxic metal continues to increase. Following exposure to mercury, this metal accumulates in numerous organs, including brain, intestine, kidneys, liver, and placenta. Although a number of mechanisms for the transport of mercuric ions into target organs were proposed in recent years, these mechanisms have not been characterized completely. This review summarizes the current literature related to the transport of inorganic and organic forms of mercury in various tissues and organs. This review identifies known mechanisms of mercury transport and provides information on additional mechanisms that may potentially play a role in the transport of mercuric ions into target cells.

Mercury (Hg) is an extremely toxic group IIB metal found in many occupational and environmental settings. This metal may exist in several different physical and chemical forms. Elemental mercury (Hg^0), for instance, exists as a liquid at room temperature, and because of its high vapor pressure, it can be released readily into the atmosphere as Hg vapor. Hg also exists as mercurous (Hg^+) or mercuric (Hg^{2+}) salts of anionic species of chlorine, sulfur, or oxygen. Of the inorganic forms of Hg, the mercuric form is the most abundant in environmental settings. Organic species of Hg are formed when a mercuric ion binds covalently with a carbon atom of an organic functional group such as a methyl, ethyl, or phenyl group. Methylmercury (CH_3Hg^+) is by far the most common form of organic Hg to which humans and animals are exposed. CH_3Hg^+ in the environment is predominantly formed by methylation of inorganic mercuric ions by microorganisms present in soil and water (Zalups, 2000; Clarkson & Magos, 2006; ATSDR, 2007; Rooney, 2007).

Since Hg is present in the environment in such a ubiquitous manner, it is virtually impossible for humans to avoid exposure to some form of Hg. In addition to environmental exposure, individuals may be exposed to Hg from dental amalgams, medicinal treatments (including vaccinations), and/or dietary sources (Geier & Geier, 2007; Kern & Jones, 2006; Dietert & Dietert, 2008) (Zalups, 2000; Clarkson & Magos, 2006; ATSDR, 2007; Risher & De Rosa, 2007). Of the different routes of exposure, most humans are exposed to Hg following ingestion of food and/or water contaminated with CH_3Hg^+ . High levels of CH_3Hg^+ are found often in large predatory freshwater and saltwater fish, such as northern pike, salmon,

swordfish, tuna, and shark (Bayen et al., 2005; Simmonds et al., 2002). Accumulation of Hg in tissues of these fish is related primarily to the predatory nature and the longevity of these fish in contaminated waters. Fish do not have the same ability to eliminate mercuric species as do mammals. Following ingestion of contaminated food and/or water, CH_3Hg^+ is absorbed readily by the gastrointestinal tract and enters the systemic circulation, where mercuric ions can be delivered to target organs (ATSDR, 2007).

Many organ systems are affected negatively by exposure to mercuric species. These include, but are not limited to, the cardiovascular (Warkany & Hubbard, 1953; Wakita, 1987; Carmignani et al., 1992; Soni et al., 1992; Wang et al., 2000), gastrointestinal (Lundgren & Swensson, 1949; Afonso & De Alvarez, 1960; Murphy et al., 1979; Bluhm et al., 1992), neurological (Jaffe et al., 1983; Lin & Lim, 1993), hepatobiliary (Murphy et al., 1979; Samuels et al., 1982; Jaffe et al., 1983), and renal (Murphy et al., 1979; Samuels et al., 1982; Rowens et al., 1991) systems.

Our current understanding of the transport of mercuric species is based on several important discoveries. First, many studies showed that the majority of mercuric ions present within biological systems are bound to molecules containing a free sulfhydryl (thiol) group. Mercuric ions rarely exist in a free, unbound state. Second, the cloning and characterization of numerous transport proteins facilitated the study of select transporters and their involvement in the uptake and secretion of mercuric species. Third, technological advances have provided investigators with the ability to study specific transport proteins, by either altering expression levels or isolating an individual transport protein. Each of these discoveries and advances has played an important role in the acquisition of the current body of knowledge, which is summarized in the following review.

BONDING CHARACTERISTICS OF MERCURIC IONS

When considering the handling of mercuric ions in biological systems, one must account for the bonding characteristics of these ions in the various body compartments of humans and other mammals. Mercuric ions have a high affinity for various nucleophilic functional groups, especially the sulfhydryl group that is present in biomolecules such as glutathione (GSH), cysteine (Cys), homocysteine (Hcy), *N*-acetylcysteine (NAC), and albumin. Due to the predilection of mercuric ions for bonding to the reduced sulfur atom of thiols, one can assume that most mercuric ions within the various tissue and fluid compartments of mammals are bound to sulfhydryl-containing molecules and thus do not exist as inorganic salts, or in an unbound, “free” ionic state (Hughes, 1957).

Inorganic mercuric ions bond with low-molecular-weight thiols in a linear II, coordinate covalent manner (Fuhr & Rabenstein, 1973; Rubino et al., 2004), while organic mercurials, such as CH_3Hg^+ , form linear I, coordinate covalent complexes with these molecules. Thiol *S*-conjugates of mercuric ions appear to be thermodynamically stable in an aqueous environment possessing a pH ranging from 1 to 14 (Fuhr & Rabenstein, 1973). The affinity constant for mercuric ions bonding to thiolate anions is on the order of 10^{15} to 10^{20} . Despite the thermodynamic stability of the coordinate covalent bonds formed between mercuric ions and various thiol-containing molecules in aqueous solution, the bonding between mercuric

ions and these thiol-containing molecules appears to be more labile within the living organism (Fuhr & Rabenstein, 1973).

Complex factors such as thiol and/or other nucleophilic competition and exchange are likely the causes of the perceived labile nature of bonding that occurs between mercuric ions and certain thiol-containing molecules in particular tissue and cellular compartments. For example, the majority of mercuric ions present in plasma (shortly after exposure to Hg^{2+}) are bound to sulfhydryl-containing proteins, such as albumin (Friedman, 1957; Mussini, 1958; Cember et al., 1968; Lau & Sarkar, 1979). Yet these mercuric ions do not remain bound to these proteins for very long, as evidenced by the rapid decrease in the plasma burden of Hg^{2+} accompanied by a rapid rate of uptake of mercuric ions in the kidneys, liver, and other organs.

More complex binding arrangements also occur between mercuric ions and protein thiols, such as the metal-containing proteins metallothionein 1 and metallothionein 2 (MT-1 and -2). In each MT-1 or MT-2 molecule, as many as seven atoms of Hg may be bonded coordinately to four sulfur atoms of cysteinyl residues (Zalups, 2000).

Current evidence indicates that mercuric *S*-conjugates of small endogenous thiols (such as Cys, Hcy, and NAC) are likely the primary transportable forms of mercury in the kidneys. Therefore, it appears that mercuric ions are transferred from plasma proteins to these low-molecular-weight thiols by a complex ligand-exchange mechanism. Moreover, the effectiveness of thiol-containing pharmacological agents, such as penicillamine, *N*-acetylpenicillamine, *meso*-2,3-dimercaptosuccinic acid (DMSA), 2,3-dimercapto-1-propanesulfonic acid (DMPS), dithioerythritol, and dithiothreitol, in reversing or protecting against adverse effects of mercury-containing compounds is based on, and can be best explained by, the ability of these agents to remove inorganic and organic mercuric ions from endogenous ligands via nucleophilic competition and exchange, leading to formation of new thiol-mercury complexes.

TRANSPORT OF INORGANIC MERCURY

Intestinal Transport of Hg^{2+}

One route of exposure to Hg^{2+} is via consumption of food and/or liquids contaminated with Hg^{2+} . Although humans can be exposed frequently to Hg^{2+} in this manner, the subsequent intestinal absorption is not a major route of absorption. It has been suggested that the means by which Hg^{2+} is transported across intestinal enterocytes depends upon the species of Hg^{2+} present in the intestinal lumen, which itself is dependent upon the ligands available to which Hg^{2+} can bind (Foulkes, 2000). Therefore, it is likely that multiple mechanisms, with varying modes of transport, are involved in the absorption of mercuric ions (Table 1). Ingested food has a high concentration of sulfhydryl-containing molecules, such as amino acids and peptides, which may bond to Hg^{2+} . Thiol *S*-conjugates of Hg^{2+} formed within the gastrointestinal tract may act as structural and/or functional homologs of select endogenous molecules, such as amino acids and/or polypeptides that are absorbed along the small intestine. Given the prevalence of amino acid and peptide transporters in enterocytes, especially along the duodenum (Ganapathy et al., 2001; Dave et al., 2004), it is possible that

thiol *S*-conjugates of Hg^{2+} are transported into cells by one or more of these carriers. Not surprisingly, the initial site of Hg^{2+} absorption appears to be the duodenum (Endo et al., 1984).

The transport of Hg^{2+} across plasma membranes of enterocytes appears to utilize passive and active mechanisms (Andres et al., 2002; Laporte et al., 2002; Hoyle & Handy, 2005). Foulkes and Bergman (1993) suggested that the intestinal absorption of Hg^{2+} is a two-step process whereby Hg^{2+} initially binds to the plasma membrane in the form of an anion such as mercuric trichloride (HgCl_3^-). Hg^{2+} then traverses the plasma membrane and is internalized. Multiple mechanisms, including amino acid, peptide, and drug and ion transporters, may play roles in this uptake. Owing to the abundance of amino acid transporters in the luminal plasma membrane of enterocytes and recent evidence implicating amino acid transporters in the transport of the Cys *S*-conjugate of Hg^{2+} , Cys-*S*-Hg-*S*-Cys, in renal proximal tubular cells (Bridges et al., 2004), one must consider that amino acid and/or peptide transporters may play significant roles in the intestinal absorption of Hg^{2+} . In contrast, MRP3, in the basolateral membrane, was found to transport a number of substrates from the intracellular compartment of enterocytes into the blood (Rost et al., 2002; Prime-Chapman et al., 2004; Shoji et al., 2004; Yokooji et al., 2007; Itagaki et al., 2008; Kitamura et al., 2009). Because of its multispecific nature and its subcellular localization, it may also play a role in the intestinal secretion of thiol *S*-conjugates of Hg^{2+} .

A small amount of Hg^{2+} may be taken up following ligand exchange whereby a mercuric ion is removed from its thiol carrier and is taken up by one or more ion transporters. One such transporter is the divalent metal transporter 1 (DMT1). This transporter is localized in the apical membrane of enterocytes (Canonne-Hergaux et al., 1999) and may play a role in the transport of mercuric ions. Although the ability of DMT1 to transport Hg^{2+} has not been shown directly, studies in mice suggest a role for DMT1 in Hg^{2+} transport in that decreased expression of intestinal DMT1 corresponded to a fall in the intestinal accumulation of Hg^{2+} (Ilback et al., 2008).

Intestinal absorption of Hg^{2+} may also involve a zinc (Zn^{2+}) carrier, such as ZIP8. In vitro studies showed that the activity of this carrier is inhibited by Cd^{2+} and Hg^{2+} (Dalton et al., 2005; He et al., 2006; Liu et al., 2008). Although it was found that ZIP8 and other ZIP proteins are present in the intestine, their exact membrane localization has not been determined. Furthermore, their ability to transport Hg^{2+} has not been shown directly.

The intestine also appears to play an important role in the elimination of Hg^{2+} in feces, either via secretion of Hg^{2+} across enterocytes via one or more transport mechanisms (Table 1), or via secretion in bile. It appears that Hg^{2+} is secreted across enterocytes by paracellular and/or transcellular mechanisms (Sugawara et al., 1998; Zalups et al., 1999a; Hoyle & Handy, 2005). Data from in vivo studies in rats with cannulated or ligated bile ducts indicate that a substantial fraction of the total pool of Hg^{2+} that is excreted in the feces is due to intestinal secretion of Hg^{2+} from blood into the intestinal lumen (Zalups, 1998c). This secretion may involve the transport of thiol *S*-conjugates of Hg^{2+} , which may act as a mimic or a functional homolog of one or more endogenous molecules secreted normally by enterocytes. Potential mechanisms for this secretion include amino acid transporters and

multidrug resistance-associated proteins (MRP). Many amino acid transporters are counter-exchangers and thus may mediate bidirectional transport of substrates. In addition, MRP2, which is present in the apical membrane of enterocytes (Maher et al., 2005), was characterized as an export protein, and as such may play a role in the export of Hg^{2+} from enterocytes into the intestinal lumen. Other members of the MRP family, including MRP4, MRP5, MRP6, and MRP7, have been identified in enterocytes (Maher et al., 2005); however, the membrane localization of these proteins is currently unknown.

Renal Transport of Hg^{2+}

The kidneys are, by far, the primary sites of mercury accumulation following exposure to elemental or inorganic forms of mercury (Adam, 1951; Ashe et al., 1953; Friberg et al., 1957; Friberg, 1959; Berlin & Gibson, 1963; Clarkson & Magos, 1966; Swensson & Ulfvarson, 1968; Cherian & Clarkson, 1976; Zalups & Diamond, 1987a, 1987b; Hahn et al., 1989, 1990; Zalups & Barfuss, 1990; Zalups, 1991a, 1991b, 1991c, 1993a). Renal uptake and accumulation of mercury in vivo occurs rapidly with as much as 50% of a low ($0.5 \mu\text{mol kg}^{-1}$) dose of Hg^{2+} present in kidneys of rats within a few hours after exposure (Zalups, 1993a).

Within the kidneys, Hg^{2+} accumulates primarily in the cortex and outer stripe of the outer medulla (Berlin & Ullberg, 1963c, 1963b, 1963a; Taugner, 1966; Zalups & Diamond, 1987a; 1987b; Zalups & Barfuss, 1990; Zalups, 1991a, 1991c, 1993a). Histochemical and autoradiographic data from mice and rats (Taugner et al., 1966; Hultman et al., 1985, 1992; Magos et al., 1985; Hultman & Enestrom, 1986, 1992; Rodier et al., 1988; Zalups, 1991a) and tubular microdissection data from rats and rabbits (Zalups & Barfuss, 1990; Zalups, 1991b) indicate that the accumulation of Hg^{2+} in the renal cortex and outer stripe of the outer medulla occurs almost exclusively along the convoluted and straight segments of the proximal tubule. Deposits of mercury have also been localized in the renal proximal tubule of monkeys exposed to elemental mercury from dental amalgams (Danscher et al., 1990). Although the proximal tubule is the primary site where mercuric ions are taken up and accumulated, there are insufficient data to exclude the possibility that other renal tubular segments may also take up, accumulate, and secrete mercuric ions.

A series of in vitro studies provides definitive evidence related to the mechanisms involved in the proximal tubular uptake of mercury. Data from these studies indicate that there are luminal and basolateral mechanisms involved in the uptake of mercuric ions by proximal tubular epithelial cells (Table 1) (Zalups & Barfuss, 1993, 1995, 1998a, 1998b; Zalups, 1995, 1997, 1998a, 1998b; Zalups & Minor, 1995; Zalups & Lash, 1997a; Wei et al., 1999; Aslamkhan et al., 2003; Bridges et al., 2004; Bridges & Zalups, 2004; Zalups & Ahmad, 2005a, 2005b, 2005c). Luminal uptake of Hg^{2+} appears to be strongly dependent upon the actions of γ -glutamyltransferase and cysteinylglycinase. Indeed, inhibition of γ -glutamyltransferase reduces significantly the renal uptake and accumulation of Hg^{2+} (Berndt et al., 1985; Tanaka et al., 1990; Tanaka-Kagawa et al., 1993; de Ceaurriz et al., 1994; Zalups, 1995). It was postulated that some GSH *S*-conjugates of Hg^{2+} (G-*S*-Hg-*S*-G) are filtered at the glomerulus and delivered into the lumen of proximal tubules, where they are

degraded rapidly and sequentially by γ -glutamyltransferase and cysteinylglycinase to yield Cys *S*-conjugates of Hg^{2+} (Cys-*S*-Hg-*S*-Cys).

In addition to the findings referenced earlier, there are several sets of data indicating that the intracellular content of GSH (and likely other thiols) exerts a significant influence on the uptake and accumulation of Hg^{2+} in renal tubular epithelial cells and hepatocytes. In the kidney, chemically induced depletion of intracellular GSH with either buthionine sulfoximine (which inhibits the γ -glutamylcysteine synthetase) or diethyl maleate (which binds GSH) was shown to decrease the accumulation of Hg^{2+} in tubular epithelial cells in both the renal cortex and outer stripe of the outer medulla (Berndt et al., 1985; Baggett & Berndt, 1986; Zalups & Lash, 1997b; Zalups et al., 1999a, 1999b). Moreover, studies in right-side-out, brush-border membrane vesicles (isolated from the renal cortex and outer stripe of the outer medulla of rats) indicate that mercuric ions are taken up more readily when they are bound to Cys than when they are conjugated to GSH or the dithiol chelator, DMPS (Zalups & Lash, 1997a). Studies using isolated perfused proximal tubules from rabbits (Cannon et al., 2000) provided additional evidence for the luminal uptake of Cys-*S*-Hg-*S*-Cys.

Subsequent experiments in isolated, perfused proximal tubules from rabbits showed that luminal uptake of Cys-*S*-Hg-*S*-Cys involves at least one Na^+ -dependent and one Na^+ -independent amino acid carrier (Cannon et al., 2001). Since Cys-*S*-Hg-*S*-Cys and the amino acid cystine are similar in size and shape, it was hypothesized that Cys-*S*-Hg-*S*-Cys may act as a molecular mimic of cystine at the site of one or more cystine transporters located in the luminal plasma membrane of proximal tubular epithelial cells. A likely candidate for the Na^+ -independent transport of Cys-*S*-Hg-*S*-Cys is system $\text{b}^{0,+}$. This heterodimeric transporter is comprised of two subunits, $\text{b}^{0,+}\text{AT}$ and rBAT, and has a high affinity for cystine and neutral and basic amino acids (Palacin et al., 1998; 2001). Recent studies utilizing type II Madin–Darby canine kidney (MDCKII) cells transfected stably with each subunit of system $\text{b}^{0,+}$ indicate that Cys-*S*-Hg-*S*-Cys and Hcy-*S*-Hg-*S*-Hcy are transportable substrates of this carrier (Bridges et al., 2004; Bridges & Zalups, 2004). In contrast, it appears that mercuric conjugates of GSH (G-*S*-Hg-*S*-G), *N*-acetylcysteine (NAC-*S*-Hg-*S*-NAC), and cysteinylglycine (CysGly; CysGly-*S*-Hg-*S*-CysGly) are not transported readily by system $\text{b}^{0,+}$ (Bridges et al., 2004). Together, these data provide strong evidence supporting the hypothesis that Cys-*S*-Hg-*S*-Cys and Hcy-*S*-Hg-*S*-Hcy act as molecular mimics or homologs of the amino acids cystine and homocystine respectively, at the site of system $\text{b}^{0,+}$.

Transport of Hg^{2+} from peritubular blood into the intracellular compartment of proximal tubular cells accounts for approximately 40–60% of proximal tubular uptake of Hg^{2+} (Zalups, 1995, 1998a, 1998b; Zalups & Barfuss, 1995, 1998a, 1998b). With in vivo experiments in rats where glomerular filtration, and hence luminal uptake, was reduced to negligible levels, the renal tubular uptake of Hg^{2+} decreased by 40% (Zalups & Minor, 1995). Based on this finding, it was suggested that the remaining uptake of Hg^{2+} occurs at the basolateral membrane (Zalups & Minor, 1995). These studies also show that when animals are treated with the organic anion *para*-aminohippurate (PAH), which specifically inhibits members of the organic anion transporter (OAT) family (Shimomura et al., 1981; Ferrier et al., 1983; Ullrich et al., 1987; Pritchard, 1988), the uptake of Hg^{2+} is inhibited

significantly. Therefore, it is likely that one or more members of the OAT family mediate a significant portion of the basolateral uptake of Hg^{2+} (Table 1). Numerous in vivo and in vitro studies provide experimental evidence indicating that mercuric conjugates of Cys, Hcy, and NAC are taken up by OAT1 and/or OAT3, which have both been localized in the basolateral plasma membrane of proximal tubular epithelial cells (Kojima et al., 2002; Motohashi et al., 2002). OAT1 appears to be the major mechanism involved in the basolateral uptake of Hg^{2+} into proximal tubular cells (Zalups & Lash, 1994; Zalups & Barfuss, 1995, 1998a, 1998b; Zalups, 1995, 1998a, 1998b). Indeed, recent findings from MDCK II cells transfected stably with OAT1 showed that Cys-S-Hg-S-Cys (Aslamkhan et al., 2003; Zalups et al., 2004), NAC-S-Hg-S-NAC (Zalups & Barfuss, 1990), and Hcy-S-Hg-S-Hcy (Zalups & Ahmad, 2004) are transportable substrates of this carrier. Additional experiments using *Xenopus laevis* oocytes implicate OAT3 in the uptake of Cys-S-Hg-S-Cys (Aslamkhan et al., 2003; Zalups et al., 2004). Taken together, the aforementioned data provide strong support for the theory that OAT1 and OAT3 play significant roles in the basolateral uptake of select mercuric species.

A substantial body of evidence has shown that mercuric ions are extracted effectively from renal tubular cells by the dithiol, metal chelators, DMPS and DMSA (Planas-Bohne, 1981; Aposhian, 1983; Aposhian et al., 1992; Zalups, 1993b; Bridges et al., 2008a, 2008b; Ruprecht, 2008; Zalups & Bridges, 2009). Although this extraction appears to involve a direct secretory process whereby mercuric ions move directly from blood into the tubular lumen (Diamond et al., 1988), the exact mechanisms involved in this process have been identified only recently (Table 1). Initial studies showed that the mechanism or mechanisms responsible for the secretion of Hg^{2+} into the lumen of proximal tubular cells required that Hg^{2+} be co-transported with GSH (Tanaka-Kagawa et al., 1993). One possible mechanism for this transport is MRP2. This carrier is localized in the luminal plasma membrane of proximal tubular cells (Schaub et al., 1997; 1999) and appears to require GSH for the transport of some substrates (Leslie et al., 2005). Indeed, indirect evidence from Eisai hyperbilirubinemic rats, which lack functional MRP2, suggests that MRP2 plays a role in the hepatobiliary secretion of Hg^{2+} (Sugawara et al., 1998). Therefore, MRP2 may play a similar role in proximal tubular epithelial cells. A study utilizing proximal tubules from killifish found that the expression of MRP2 increases after exposure to HgCl_2 (Terlouw et al., 2002), suggesting that mercuric ions somehow enhance transcription of the *mrp2* gene. The ability of MRP2 to transport Hg^{2+} , however, was not measured directly. In addition, in this study proximal tubules were exposed to Hg^{2+} as HgCl_2 , which is not a physiologically relevant form of Hg^{2+} . Under normal in vivo conditions, Hg^{2+} is usually bound to one or more thiol-containing molecules. A more recent study utilized MRP2-deficient (TR^-) rats to study the role of MRP2 in the secretion of mercuric ions. Rats were exposed initially to HgCl_2 and, in order to facilitate the secretion of mercuric ions, were treated subsequently with DMPS or DMSA. These studies demonstrated that MRP2 plays a significant role in the secretion of mercuric ions and the following model for the DMPS- and DMSA-mediated extraction of mercuric ions was proposed (Bridges et al., 2008a, 2008b). DMPS and DMSA are thought to be taken up at the basolateral membrane of proximal tubular cells via OAT1 and the sodium-dependent dicarboxylate transporter (NaC2), respectively (Islinger et al., 2001; Bahn et al., 2002; Burckhardt et al., 2002). Once internalized, DMPS and DMSA

likely form complexes with intracellular Hg^{2+} ; these complexes appear to be exported by MRP2 across the luminal plasma membrane of proximal tubular cells into the tubular lumen. Indeed, studies utilizing membrane vesicles prepared from Sf9 cells transfected with human MRP2 provided direct evidence that MRP2 is able to transport both DMPS- and DMSA-S-conjugates of Hg^{2+} (Bridges et al., 2008a, 2008b). Although data from studies in other organs and experimental systems suggest that secretion of mercuric ions via MRP2 requires co-transport of GSH, current renal data do not indicate that co-transport of GSH is required for export of mercuric ions from proximal tubular cells.

Hepatic Transport of Hg^{2+}

Shortly after exposure to Hg^{2+} , mercuric ions in sinusoidal blood are likely bound mainly to plasma proteins (like albumin, ferritin, and γ -globulins) and, to a lesser degree, several nonprotein thiols. There are a few potential mechanisms that can explain the uptake of Hg^{2+} across the sinusoidal membrane of hepatocytes (Table 1). One of these mechanisms is endocytosis. Fluid-phase, absorptive and receptor-mediated endocytotic processes are involved in the uptake of extracellular molecules (present in sinusoidal blood) into hepatocytes. Significant amounts of fluid uptake and membrane turnover in hepatocytes occur by fluid-phase and receptor-mediated endocytosis (Oka et al., 1989). As is the case with iron (Fe), mercuric ions may gain entry into hepatocytes via endocytosis mediated by one of the Fe-binding proteins and/or albumin. As a matter of fact, ferritin appears to bind Cd, Zn, Be, and Al. Thus, endocytosis of Hg-ferritin or Hg-albumin complexes may indeed serve as a route of entry of Hg^{2+} into hepatocytes. It has actually been suggested that ferritin may serve a detoxifying protein due its ability to bind a number of cationic forms of several elements (Joshi et al., 1989).

Since Hg^{2+} forms thermodynamically stable complexes with GSH and/or amino acids, such as Cys and Hcy, these complexes may enter hepatocytes via transporters that mediate uptake of structurally similar endogenous compounds. Within the sinusoidal membrane of hepatocytes, several members of the MRP family that transport conjugates of GSH have been identified (Ballatori et al., 2005; Deeley et al., 2006). However, transport of Hg^{2+} by these isoforms has not been studied. Furthermore, since these carriers have been characterized as export proteins, it is not clear whether they are capable of mediating uptake of substrates from blood into hepatocytes. In addition to GSH transporters, numerous amino acid carriers have been identified in the liver (Bode, 2001; Wagner et al., 2001), yet it is currently unclear which, if any, of these carriers are present in the sinusoidal membrane.

Unlike transport at the sinusoidal plasma membrane, transport of Hg^{2+} across the canalicular plasma membrane of hepatocytes has been studied quite extensively. Early studies suggest that hepatobiliary transport of Hg^{2+} is dependent upon hepatocellular concentrations of GSH (Ballatori & Clarkson, 1983, 1984, 1985a, 1985b; Dutczak & Ballatori, 1992; Zalups & Lash, 1997b). Indeed, when GSH levels in rats were decreased artificially, hepatocellular retention and/or uptake of intravenously administered Hg^{2+} increased significantly (Zalups & Lash, 1997). These findings suggest that when cytosolic GSH is low, mercuric ions are unable to exit hepatocytes efficiently. Consequently, mercuric ions accumulate in intracellular compartments of hepatocytes. These data also indicate that intracellular levels

of GSH play an important role in the transport of Hg^{2+} out of hepatocytes. The exact mechanisms involved in the hepatobiliary transport of mercuric ions have not been identified; however, experimental evidence suggests that Hg^{2+} , as a conjugate of GSH, is exported across the canalicular membrane. Since G-S-Hg-S-G is similar structurally to GSSG, it may be taken up by a GSSG transporter. MRP2 appears to transport GSSG and is present in the canalicular membrane of hepatocytes (Akerboom et al., 1991; Buchler et al., 1996; Keppler & Konig, 1997). Recently, MRP2 has been implicated in the transport of Hg^{2+} as a conjugate of DMPS or DMSA (Bridges et al., 2008a, 2008b). Therefore, it is likely that this carrier may also mediate the transport of other species of Hg^{2+} (Table 1).

Transport of Hg^{2+} in the Placenta

Maternal exposure to organic forms of Hg is clearly more toxic to developing fetuses than exposure to Hg^{2+} . However, mercuric ions accumulate in placentas of pregnant women exposed to Hg^{2+} and may be detrimental to the fetus (Inouye & Kajiwara, 1990; Ask et al., 2002). Surprisingly, the mechanisms by which Hg^{2+} is transported across the placenta are not well defined. Experiments in brush-border membrane vesicles from human placenta suggest that an amino acid transporter may be involved in the placental transport of Hg^{2+} (Iioka et al., 1987). However, since these studies used HgCl_2 instead of a more physiologically relevant species of Hg^{2+} , such as Cys-S-Hg-S-Cys, these findings may not truly represent processes occurring in vivo. Even so, considering these data and the prevalence of amino acid transporters in the placenta (Jansson, 2001; Kudo & Boyd, 2002), it is postulated that Hg^{2+} , when bound to a Cys or Hcy, may be transported across apical and basolateral membranes of placental epithelial cells via one or more amino acid transporters (Table 1). Other transporters, such as OAT4, may mediate the transport of mercuric ions from the fetal circulation into placental trophoblasts; however, the ability of OAT4 to mediate the transport of mercuric species has not been examined. On the apical plasma membrane, MRP2 may mediate the transport of mercuric species from within placental trophoblasts into maternal circulation (Table 1).

TRANSPORT OF METHYLMERCURY

Transport of CH_3Hg^+ in the Brain

Clinically relevant adverse effects of CH_3Hg^+ occur in the brain and central nervous system (CNS) (WHO, 2000; ATSDR, 2007). Therefore, it is not surprising that a large number of studies have focused on mechanisms by which CH_3Hg^+ gains access to the CNS, specifically, how CH_3Hg^+ crosses the blood–brain barrier. Similar to Hg^{2+} , CH_3Hg^+ does not exist as a free, unbound cation in biological systems (Hughes, 1957), but rather is found conjugated to thiol-containing biomolecules, such as GSH, Cys, Hcy, NAC, or albumin (Clarkson, 1993). Early studies utilizing homogenates of rat cerebrum demonstrated that GSH is the primary nonprotein thiol bound to CH_3Hg^+ (Thomas & Smith, 1979). Subsequent studies in rats and primary cultures of bovine brain endothelial cells showed that co-administration of Cys with CH_3Hg^+ increased the uptake of CH_3Hg^+ into capillary endothelial cells of the blood–brain barrier (Hirayama, 1980; Aschner & Clarkson, 1988, 1989). Interestingly, the uptake of CH_3Hg^+ into cells was inhibited significantly by the presence of the neutral amino acid phenylalanine (Hirayama, 1975, 1980, 1985; Thomas &

Smith, 1982). In vivo studies in rat brain (Aschner & Clarkson, 1988) and in vitro studies in bovine cerebral capillary endothelial cells (Aschner & Clarkson, 1989) demonstrated that neutral amino acids are capable of inhibiting the uptake of $\text{CH}_3\text{Hg-S-Cys}$. These data collectively led to the hypothesis that Cys *S*-conjugates of CH_3Hg^+ ($\text{CH}_3\text{Hg-S-Cys}$) are transportable substrates of a neutral amino acid transporter in the capillary endothelium of the blood–brain barrier. It was suggested that the structural similarities between $\text{CH}_3\text{Hg-S-Cys}$ and methionine (Landner, 1971; Jernelov, 1973) allow this species of CH_3Hg^+ to cross the blood–brain barrier. One possible mechanism for this transport is the amino acid carrier, system L (Table 2) (Wagner et al., 2001).

System L is a heterodimeric protein, comprised of a heavy chain, 4F2hc, and a light chain, LAT1 or LAT2, bound together by a disulfide bond (Chillaron et al., 2001; Wagner et al., 2001). LAT1 and LAT2 have been localized in the apical and basolateral plasma membranes, respectively, of endothelial cells lining the blood–brain barrier (Betz & Goldstein, 1978). System L is capable of transporting a broad range of substrates (Oldendorf, 1973). Thus, it is possible that this carrier may also utilize $\text{CH}_3\text{Hg-S-Cys}$ as a substrate. Indeed, in vivo studies in rats (Kerper et al., 1992) and in vitro studies utilizing primary cultures of rat astrocytes (Aschner et al., 1990; 1991) suggest that $\text{CH}_3\text{Hg-S-Cys}$ is a transportable substrate of system L. Subsequent studies showed that Hcy *S*-conjugates of CH_3Hg^+ ($\text{CH}_3\text{Hg-S-Hcy}$) may also be substrates of system L (Mokrzan et al., 1995). Specific studies of LAT1 and LAT2 in *Xenopus laevis* oocytes provide the first direct molecular evidence showing that $\text{CH}_3\text{Hg-S-Cys}$ is a transportable substrate of LAT 1 and 2 (Simmons-Willis et al., 2002). These data also provide substantive evidence for the phenomenon of molecular mimicry in that $\text{CH}_3\text{Hg-S-Cys}$ appears to mimic methionine at the site of system L.

Transport of CH_3Hg^+ in Erythrocytes

The handling of mercuric ions, specifically GSH *S*-conjugates of CH_3Hg^+ ($\text{CH}_3\text{Hg-S-G}$), has also been studied in erythrocytes. Wu (1995) reported that when experiments were performed at 5°C, multiple transport systems appeared to be involved in the uptake of $\text{CH}_3\text{Hg-S-G}$. The primary mechanism for this transport was postulated to be a member of the OAT family. Additional mechanisms may include a D-glucose diffusive transporter, a cysteine-facilitated transporter, and/or a Cl^- transporter (Table 2) (Wu, 1995). Because these experiments were carried out at 5°C, it is possible that the mechanisms for $\text{CH}_3\text{Hg-S-G}$ transport that were identified in the aforementioned study may differ from those responsible for this uptake at physiological temperatures. In subsequent studies, the uptake of $\text{CH}_3\text{Hg-S-G}$ was measured at 5°C and 20°C, and it was suggested that a member of the OAT family was the primary mechanism responsible for $\text{CH}_3\text{Hg-S-G}$ uptake at both temperatures (Wu, 1996). Subsequent studies showed that the uptake of $\text{CH}_3\text{Hg-S-G}$ was inhibited by probenecid, which suggested that this conjugate is a transportable substrate of OAT (Wu, 1997). It should be noted, however, that probenecid is not a specific inhibitor of OAT. Wu (1997) reported that system N, system γ^+ , and the oligopeptide H^+ transport system were not involved in the uptake of $\text{CH}_3\text{Hg-S-G}$.

Intestinal Transport of CH_3Hg^+

As mentioned previously, humans are exposed to CH_3Hg^+ primarily through the ingestion of contaminated food and/or water. Unlike the intestinal absorption of Hg^{2+} , absorption of CH_3Hg^+ by intestinal enterocytes is more efficient. Therefore, it is important that the mechanisms involved in the intestinal absorption of CH_3Hg^+ are understood thoroughly. A number of various mechanisms may be involved in this process (Table 2). Urano and colleagues (1990) suggested that there are two independent transport systems for the uptake of CH_3Hg^+ , when it is presented to enterocytes as $\text{CH}_3\text{Hg-S-G}$. Since the luminal uptake of CH_3Hg^+ can be inhibited by acivicin (an alkylator of γ -glutamyltransferase) and probenecid (a known inhibitor of OAT), it was suggested that one mode of CH_3Hg^+ uptake into enterocytes is dependent upon the activity of γ -glutamyltransferase, while the other appears to involve one or more members of the OAT family. As noted earlier, probenecid is not a specific inhibitor of OAT, and thus, may inhibit other transporters. Currently, only OAT2 and OAT10 have been detected in the intestine (Hilgendorf et al., 2007; Bahn et al., 2008); the membrane localization of either protein has not been examined. In addition, several members of the OATP family (Hilgendorf et al., 2007) and a novel organic anion transporter-like protein (OATLP1) are present in the intestine (Jung et al., 2006). Currently, there are no published data regarding the ability of these carriers to transport mercuric ions.

Despite the apparent ability of $\text{CH}_3\text{Hg-S-G}$ to be taken up by enterocytes, it appears that CH_3Hg^+ is absorbed more readily when it is conjugated to one of the products of GSH catabolism (i.e., CysGly or Cys) (Urano et al., 1990). Indeed, when the activity of γ -glutamyltransferase was inhibited, the transport of $\text{CH}_3\text{Hg-S-G}$ into enterocytes was reduced by 50%. The CysGly-S-conjugate of CH_3Hg^+ ($\text{CH}_3\text{Hg-S-CysGly}$), which is the first product following the action of γ -glutamyltransferase on $\text{CH}_3\text{Hg-S-G}$, is likely degraded further at the luminal plasma membrane of enterocytes to yield $\text{CH}_3\text{Hg-S-Cys}$. Any $\text{CH}_3\text{Hg-S-CysGly}$ that escapes degradation, however, may be taken up into cells via a peptide transporter present in the luminal plasma membrane. In the intestine, di- and tripeptide transporters are the primary means for the uptake of amino acids. Considering this, and the structural resemblance of $\text{CH}_3\text{Hg-S-CysGly}$ to a small peptide, it is possible that this complex mimics an endogenous di- or tripeptide in order to cross the luminal membrane of enterocytes. In contrast, $\text{CH}_3\text{Hg-S-Cys}$, which appears to be the primary species of CH_3Hg^+ secreted into the intestine from bile, is absorbed rapidly by enterocytes (Norseth & Clarkson, 1971), possibly by one of the many amino acid carriers present in the luminal membrane of enterocytes.

Clearly, CH_3Hg^+ is transported out of enterocytes at the basolateral membrane and subsequently enters the circulation (Leaner & Mason, 2002). Unfortunately, the mechanisms involved in this transport remain unclear. It was suggested that the basolateral efflux of CH_3Hg^+ involves one or more active-transport carrier proteins. Indeed, competitive inhibition experiments in isolated, perfused catfish intestines provide indirect evidence suggesting a role for a neutral amino acid transporter in the basolateral flux of $\text{CH}_3\text{Hg-S-Cys}$ from intestinal enterocytes. Since system L was implicated in the transport of $\text{CH}_3\text{Hg-S-Cys}$ in other cell types and organs, and because of its basolateral localization in enterocytes (Dave et al., 2004), it is a likely candidate for the export of mercuric species.

Alternatively, Foulkes (1993) suggested that intracellular concentrations of GSH play an important role in regulating the basolateral efflux of CH_3Hg^+ from enterocytes into the circulation. Owing to structural similarities between $\text{CH}_3\text{Hg-S-G}$ and GSH, it may be postulated that a GSH transporter, such as MRP3, may play a role in the basolateral efflux of $\text{CH}_3\text{Hg-S-G}$.

Renal Transport of CH_3Hg^+

CH_3Hg^+ is capable of inducing significant detrimental effects in the kidney (Prickett et al., 1950; Friberg, 1959; Norseth & Clarkson, 1970a, 1970b; Magos & Butler, 1976; Magos et al., 1981, 1985; McNeil et al., 1988), even though the level of accumulation, following acute exposures, is much less than the level that occurs after exposure to inorganic or elemental forms of mercury. Until recently, the mechanism by which CH_3Hg^+ is taken up by renal tubular epithelial cells remained unknown. Early studies showed that the renal tubular uptake of CH_3Hg^+ is dependent upon intracellular concentrations of GSH (Richardson & Murphy, 1975). Several additional studies demonstrated that the renal uptake and accumulation of CH_3Hg^+ increases following co-administration of CH_3Hg^+ and GSH (Alexander & Aaseth, 1982; Tanaka et al., 1992). It has also been suggested that γ -glutamyltransferase and cysteinylglycinase, which are both present in the luminal membrane of proximal tubular cells, act upon $\text{CH}_3\text{Hg-S-G}$ to yield $\text{CH}_3\text{Hg-S-Cys}$ (Zalups, 2000), which is likely the most transportable form of CH_3Hg^+ . It is important to note that during the catabolism of GSH, the methylmercuric ion remains bound to the sulfur atom of Cys (Naganuma et al., 1988). When the activity of γ -glutamyltransferase was inhibited by acivicin, the uptake of CH_3Hg^+ into renal tubules decreased while the urinary excretion of GSH and CH_3Hg^+ increased (Berndt et al., 1985; Mulder & Kostyniak, 1985; Gregus et al., 1987; Naganuma et al., 1988; Yasutake et al., 1989; de Ceaurriz & Ban, 1990; Di Simplicio et al., 1990; Tanaka et al., 1990, 1991, 1992). In addition, in vivo studies in mice deficient in γ -glutamyltransferase showed that less CH_3Hg^+ was absorbed by renal tubular cells (Ballatori et al., 1998). These data indicate that the catabolism of $\text{CH}_3\text{Hg-S-G}$ is required for the luminal absorption of CH_3Hg^+ by proximal tubular cells and support the theory that $\text{CH}_3\text{Hg-S-Cys}$ is the most readily transportable species of CH_3Hg^+ .

$\text{CH}_3\text{Hg-S-Cys}$ and methionine are similar structurally; therefore, it is possible that both compounds are transported by the same carrier. Thus, it is not surprising to find that the amino acid transporter, system $\text{B}^{0,+}$ is capable of mediating the transport of CH_3Hg^+ as a conjugate of Cys or Hcy ($\text{CH}_3\text{Hg-S-Hcy}$; Table 2) (Bridges & Zalups, 2006). System $\text{B}^{0,+}$ is localized in the luminal plasma membrane of proximal tubular cells (Gonska et al., 2000) and mediates the Na^+ -dependent transport of many neutral and cationic amino acids, including Met (Sloan & Mager, 1999; Nakanishi et al., 2001). Studies using *Xenopus laevis* oocytes indicate that system $\text{B}^{0,+}$ is capable of transporting $\text{CH}_3\text{Hg-S-Cys}$ and $\text{CH}_3\text{Hg-S-Hcy}$ in a concentration- and time-dependent manner (Bridges & Zalups, 2006). Uptake of each mercuric species was inhibited by known substrates for system $\text{B}^{0,+}$. It is interesting to note that the substrate specificity of system $\text{B}^{0,+}$ is similar to that of system $\text{b}^{0,+}$, which was found to transport conjugates of Hg^{2+} (Bridges et al., 2004; Bridges & Zalups, 2004).

In addition to mechanisms on the luminal plasma membrane, there are also basolateral mechanisms involved the renal tubular uptake of CH_3Hg^+ (Tanaka et al., 1992). Basolateral transport of CH_3Hg^+ from the peritubular capillaries into proximal tubular cells is thought to involve a multispecific carrier, such as the organic anion transporter 1 (OAT1; Table 2). OAT1 is localized exclusively in the basolateral membrane of proximal tubular epithelial cells (Kojima et al., 2002; Motohashi et al., 2002) and mediates the uptake of Cys-, Hcy-, NAC- and DMPS-*S*-conjugates of CH_3Hg^+ (Koh et al., 2002; Zalups & Ahmad, 2005a, 2005b, 2005c).

Interestingly, several studies showed that a significant fraction of Hg in the kidneys of animals exposed to methylmercury is in the inorganic form (Gage, 1964; Norseth & Clarkson, 1970a, 1970b; Omata et al., 1980; Magos et al., 1985; Rodier et al., 1988). These findings suggest that organic mercury is oxidized to inorganic mercury prior to and/or after it enters the renal tubular epithelial cells. In addition, some evidence suggests that methylmercury is converted intracellularly to Hg^{2+} (Dunn & Clarkson, 1980). The mechanism responsible for this conversion, however, is unknown currently.

It is well documented that the metal chelators DMPS and DMSA are capable of extracting mercuric ions following exposure to CH_3Hg^+ (Aposhian, 1983; Aposhian et al., 1992). The mechanisms by which this extraction occurs have been unclear until recently. In vivo studies in MRP2-deficient (TR^-) rats exposed to CH_3Hg^+ and treated subsequently with NAC, DMPS, or DMSA provide support for the hypothesis that MRP2 mediates the transport of CH_3Hg^+ from within proximal tubular cells into the tubular lumen (Table 2) (Madejczyk et al., 2007; Zalups & Bridges, 2009). Experiments using membrane vesicles isolated from kidneys of TR^- rats provided more direct evidence suggesting that $\text{CH}_3\text{Hg-S-NAC}$ is a transportable substrate of MRP2 (Madejczyk et al., 2007). Additional experiments using inside-out membrane vesicles from Sf9 cells transfected with human MRP2 also provide direct evidence indicating that DMPS- and DMSA-*S*-conjugates of CH_3Hg^+ are transportable substrates of MRP2 (Zalups & Bridges, 2009). Collectively, these data provide strong support for the hypothesis that MRP2 plays a significant role in the renal elimination of mercuric ions following exposure to CH_3Hg^+ with subsequent chelation therapy.

Hepatic Transport of CH_3Hg^+

Following absorption by the intestine, CH_3Hg^+ is delivered to the liver via portal blood. Little is known about the mechanisms by which CH_3Hg^+ is transported into hepatocytes at the sinusoidal membrane. In vivo studies in rats showed that hepatic uptake and accumulation of CH_3Hg^+ was enhanced when Cys or GSH was either co-administered with or subsequently administered to CH_3Hg^+ (Thomas & Smith, 1982), suggesting that amino acid carriers and/or a GSH transporter may be involved in this process (Table 2). More recently, an in vitro study using a human hepatic cell line (HepG2 cells) demonstrated that cellular uptake of CH_3Hg^+ occurs more rapidly when cells are exposed to CH_3Hg^+ as a conjugate of Cys (Wang et al., 2000). The specific mechanisms involved in this transport remain unknown.

The transport of CH_3Hg^+ across the canalicular membrane has been studied more extensively and is better defined. Findings from numerous studies indicate that transport of

CH_3Hg^+ from hepatocytes into the biliary canaliculus occurs in association with GSH (Refsvik & Norseth, 1975; Ballatori & Clarkson, 1982, 1983, 1985a, Refsvik, 1982). This is not surprising since the majority of CH_3Hg^+ within hepatocytes appears to be bound to GSH (Omata et al., 1978). Interestingly, increased hepatocellular levels of GSH correspond to a rise in the excretion of GSH and CH_3Hg^+ into bile (Magos et al., 1978). In contrast, a reduction in the hepatic and biliary levels of GSH corresponds to a reduced accumulation of CH_3Hg^+ in liver (Refsvik, 1978). Therefore, it seems that the intracellular concentration of GSH significantly impacts the hepatic transport of CH_3Hg^+ . It may be postulated that $\text{CH}_3\text{Hg-S-G}$, formed within hepatocytes, is transported across the canalicular membrane into bile. Since $\text{CH}_3\text{Hg-S-G}$ is similar structurally to GSH, it is possible that this conjugate may utilize a GSH transporter in the canalicular membrane for export out of hepatocytes (Table 2). Indeed, Dutczak and Ballatori (1994) suggested that a GSH transport system in the canalicular membrane plays a significant role in the biliary secretion of $\text{CH}_3\text{Hg-S-G}$. MRP2, which is capable of transporting GSH, has since been identified in the canalicular membrane of hepatocytes (Fernandez-Checa et al., 1992, 1993; Garcia-Ruiz et al., 1992; Ballatori & Dutczak, 1994; Ballatori & Truong, 1995) and thus likely plays an important role in the export of CH_3Hg^+ . Indeed, recent studies in TR^- rats indicate that MRP2 plays a role in the hepatobiliary elimination of mercuric ions following exposure to CH_3Hg^+ (Table 2) (Madejczyk et al., 2007; Zalups & Bridges, 2009).

After secretion into bile, $\text{CH}_3\text{Hg-S-G}$ appears to be hydrolytically catabolized in a sequential manner by the plasma membrane enzymes γ -glutamyltransferase and cysteinylglycinase to yield $\text{CH}_3\text{Hg-S-Cys}$, which can be reabsorbed, both by cells lining the bile ducts and by enterocytes in the intestine (Dutczak et al., 1991; Dutczak & Ballatori, 1992; Ballatori, 1994). Though the actual mechanisms involved in the uptake of mercuric ions along the biliary tree have not been determined, it is reasonable to hypothesize that $\text{CH}_3\text{Hg-S-Cys}$ utilizes one or more amino acid transporters in order to gain access to cells. A number of various amino acid transporters, including system L (LAT3) (Babu et al., 2003), are present in the liver and biliary tree (Bode, 2001; Wagner et al., 2001); however, the exact membrane localization of each carrier has not been reported.

Transport of CH_3Hg^+ in the Placenta

The deleterious effects of CH_3Hg^+ on fetal development have been recognized widely as one of the most serious toxicological consequences of CH_3Hg^+ exposure (Matsumoto et al., 1965; Amin-Zaki et al., 1974; Harada, 1978; 1995; Kajiwara & Inouye, 1986; Inouye & Kajiwara, 1988; Kajiwara & Inouye, 1992; Davidson et al., 2008). Following maternal exposure to CH_3Hg^+ , mercuric ions are taken up readily by the placenta and accumulate subsequently in both placental and fetal tissues (Inouye et al., 1985; Inouye & Kajiwara, 1988; Ask et al., 2002). Despite the clinical significance of this area, little is known about the mechanism(s) by which mercuric ions are taken up and transported across the placenta. In vivo studies (Kajiwara et al., 1996) showed that CH_3Hg^+ is transported across the rat placenta by a neutral amino acid carrier in a time- and dose-dependent manner. Interestingly, co-administration of CH_3Hg^+ with methionine increased the placental burden of CH_3Hg^+ . It was proposed that this increase in uptake may be the result of the intracellular conversion of methionine to Cys, which may subsequently combine with CH_3Hg^+ to form a transportable

species of CH_3Hg^+ , i.e., $\text{CH}_3\text{Hg-S-Cys}$. This conjugate may utilize a neutral amino acid carrier such as system L in order to gain access to placenta trophoblasts. Since the two isoforms of system L, LAT1 and LAT2, appear to mediate the transport of $\text{CH}_3\text{Hg-S-Cys}$ in astrocytes and across epithelial cells of the blood–brain barrier (Aschner et al., 1990; Kerper et al., 1992; Mokrzan et al., 1995; Simmons-Willis et al., 2002), it is logical to postulate that this same carrier may also be involved in the transport of $\text{CH}_3\text{Hg-S-Cys}$ across the placenta (Table 2). In the placenta, LAT1 is localized in the apical (maternal) plasma membrane of trophoblasts while LAT2 is found in the basolateral (fetal) membrane (Kudo & Boyd, 2002). A number of other carrier systems (e.g., amino acid, organic anion) are present in the placenta (Leazer & Klaassen, 2003), and although the roles of these other transporters in the transport of CH_3Hg^+ have not been examined, they should be considered as possible mechanisms for this transport (Table 2).

The mechanisms on the basolateral membrane of trophoblasts that mediate the uptake of mercuric ions from fetal circulation into the placenta have not been identified. One possible mechanism is OAT4, which is localized in the basolateral membrane of placental trophoblasts (Table 2) (Cha et al., 2000; St-Pierre et al., 2000). Since other members of the OAT family transport mercuric ions, it is possible that OAT4 may also be capable of mediating the transport of mercuric species. To date, the ability of OAT4 to transport mercuric ions has not been reported.

Recently, the ability of different chelators to extract mercuric ions from placental and fetal tissues was examined. In pregnant rats exposed to CH_3Hg^+ , treatment with NAC, DMPS, or DMSA facilitates the extraction of mercuric ions from fetal and placental tissues (Aremu et al., 2008; Bridges et al., 2009). OAT4 may be responsible for mediating the transport of mercuric species from fetal tissues, across the basolateral membrane of placental trophoblasts into the intracellular compartments of these cells. On the apical membrane, MRP2, which is localized in the apical membrane of trophoblasts (St-Pierre et al., 2000), may mediate the placental to maternal transfer of mercuric ions (Table 2). Currently, there are no direct data to support these theories.

CONCLUSIONS

In writing this review, every effort has been made to summarize the current literature related to the transport of mercuric ions in various organ systems and tissues. Published studies provide strong evidence for the involvement of amino acid, anion, and drug transporters in the uptake and secretion of mercuric ions in various organs and tissues. Despite the growing body of literature pertaining to the handling of various species of mercury within the body, there remain numerous gaps in our knowledge. This lack of knowledge may be due, in part, to the difficulties associated with working with mercuric species. For example, the chemical bonding nature of mercury often complicates experiments because of bonding to plasma membranes and intracellular proteins.

Not surprisingly, the majority of research to date focused on mechanisms by which Hg^{2+} and CH_3Hg^+ are transported within their target organs, i.e., the kidney and brain, respectively. In contrast, little is known about the mechanisms by which mercuric ions are transported by

cells of other organs. Although it is clear that intestinal absorption of Hg^{2+} and CH_3Hg^+ occurs, the exact mechanisms involved in the uptake and secretion of mercuric ions by enterocytes have not been identified. In addition, hepatic handling of mercuric species has not been elucidated fully. Mechanisms for the handling of mercuric ions have been identified on the canalicular membrane of hepatocytes, yet the mechanisms that allow mercuric ions to enter hepatocytes at the sinusoidal membrane remain unclear. Furthermore, little is known about the transport of mercuric ions across the placenta, despite the clinical significance of this area of research.

Given the lack of clarity regarding the movement of mercuric ions across cellular plasma membranes, it is clear that a great deal of research is still required in order to understand completely the mechanisms involved in the transport of mercury. Experiments utilizing models such as knockout animals, transfected cells, membrane vesicles, and *Xenopus laevis* oocytes expressing specific transporters will be necessary to characterize the mechanisms involved in the uptake and secretion of mercuric species by cells of various organs. A thorough understanding of both these mechanisms and the way in which mercury is handled at the cellular and molecular levels may lead to advances in treatment regimes for patients intoxicated by mercury, as well a better understanding of the nature and function of various transport proteins of vital substrates.

Acknowledgments

This work was supported by grants from the National Institutes of Health (National Institute of Environmental Health Sciences) awarded to C. C. Bridges (ES015511) and R. K. Zalups (ES05980 and ES11288).

REFERENCES

- Adam KR 1951 The effects of dithiols on the distribution of mercury in rabbits. *Br. J. Pharmacol. Chemother* 6:483–491. [PubMed: 14878984]
- Afonso JF and De Alvarez RR 1960 Effects of mercury on human gestation. *Am. J. Obstet. Gynecol* 80:145–154. [PubMed: 13791975]
- Akerboom TP, Narayanaswami V, Kunst M, and Sies H 1991 ATP-dependent S-2,4-dinitrophenylglutathione transport in canalicular plasma membrane vesicles from rat liver. *J. Biol. Chem* 266:13147–13152. [PubMed: 2071597]
- Alexander J, and Aaseth J 1982 Organ distribution and cellular uptake of methyl mercury in the rat as influenced by the intra- and extracellular glutathione concentration. *Biochem. Pharmacol* 31:685–690. [PubMed: 7082336]
- Amin-Zaki L, Elhassani S, Majeed MA, Clarkson TW, Doherty RA, and Greenwood M 1974 Intra-uterine methylmercury poisoning in Iraq. *Pediatrics* 54:587–595. [PubMed: 4480317]
- Andres S, Laporte JM, and Mason RP 2002 Mercury accumulation and flux across the gills and the intestine of the blue crab *Callinectes sapidus*. *Aquat. Toxicol* 56:303–320. [PubMed: 11856578]
- Aposhian HV 1983 DMSA and DMPS—Water soluble antidotes for heavy metal poisoning. *Annu. Rev. Pharmacol. Toxicol* 23:193–215. [PubMed: 6307120]
- Aposhian HV, Maiorino RM, Rivera M, Bruce DC, Dart RC, Hurlbut KM, Levine DJ, Zheng W, Fernando Q, Carter D, and Aposhian MM 1992 Human studies with the chelating agents, DMPS and DMSA. *J. Toxicol. Clin. Toxicol* 30:505–528. [PubMed: 1331491]
- Aremu DA, Madejczyk MS, and Ballatori N 2008 *N*-Acetylcysteine as a potential antidote and biomonitoring agent of methylmercury exposure. *Environ. Health Perspect* 116:26–31. [PubMed: 18197295]

- Aschner M, and Clarkson TW 1988 Uptake of methylmercury in the rat brain: Effects of amino acids. *Brain Res.* 462:31–39. [PubMed: 3179736]
- Aschner M, and Clarkson TW 1989 Methyl mercury uptake across bovine brain capillary endothelial cells in vitro: the role of amino acids. *Pharmacol. Toxicol* 64:293–297. [PubMed: 2498864]
- Aschner M, Eberle NB, Goderie S, and Kimelberg HK 1990 Methylmercury uptake in rat primary astrocyte cultures: The role of the neutral amino acid transport system. *Brain Res.* 521:221–228. [PubMed: 2207661]
- Aschner M, Eberle NB, and Kimelberg HK 1991 Interactions of methylmercury with rat primary astrocyte cultures: Methylmercury efflux. *Brain Res.* 554:10–14. [PubMed: 1933294]
- Ashe WF, Largent EJ, Dutra FR, Hubbard DM, and Blackstone M 1953 Behavior of mercury in the animal organism following inhalation. *AMA Arch. Ind. Hyg. Occup. Med* 7:19–43. [PubMed: 13007198]
- Ask K, Akesson A, Berglund M, and Vahter M 2002 Inorganic mercury and methylmercury in placentas of Swedish women. *Environ. Health Perspect* 110:523–526. [PubMed: 12003757]
- Aslamkhan AG, Han YH, Yang XP, Zalups RK, and Pritchard JB 2003 Human renal organic anion transporter 1-dependent uptake and toxicity of mercuricthiol conjugates in Madin-Darby canine kidney cells. *Mol. Pharmacol* 63:590–596. [PubMed: 12606766]
- ATSDR. 2007 Toxicological profile for mercury. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control.
- Babu E, Kanai Y, Chairoungdua A, Kim DK, Iribe Y, Tangtrongsup S, Jutabha P, Li Y, Ahmed N, Sakamoto S, Anzai N, Nagamori S, and Endou H 2003 Identification of a novel system L amino acid transporter structurally distinct from heterodimeric amino acid transporters. *J. Biol. Chem* 278:43838–43845. [PubMed: 12930836]
- Baggett JM, and Berndt WO 1986 The effect of depletion of nonprotein sulfhydryls by diethyl maleate plus buthionine sulfoximine on renal uptake of mercury in the rat. *Toxicol. Appl. Pharmacol* 83:556–562. [PubMed: 3705075]
- Bahn A, Hagos Y, Reuter S, Balen D, Brzica H, Krick W, Burckhardt BC, Sabolic I, and Burckhardt G 2008 Identification of a new urate and high affinity nicotinate transporter, hOAT10 SLC22A13. *J. Biol. Chem* 283:16332–16341. [PubMed: 18411268]
- Bahn A, Knabe M, Hagos Y, Rodiger M, Godehardt S, Graber-Neufeld DS, Evans KK, Burckhardt G, and Wright SH 2002 Interaction of the metal chelator 2,3-dimercapto-1-propanesulfonate with the rabbit multispecific organic anion transporter 1 rOAT1. *Mol. Pharmacol* 62:1128–1136. [PubMed: 12391276]
- Ballatori N 1994 Glutathione mercaptides as transport forms of metals. *Adv. Pharmacol* 27:271–298. [PubMed: 8068556]
- Ballatori N, and Clarkson TW 1982 Developmental changes in the biliary excretion of methylmercury and glutathione. *Science* 216:61–63. [PubMed: 7063871]
- Ballatori N, and Clarkson TW 1983 Biliary transport of glutathione and methyl mercury. *Am. J. Physiol* 244:G435–G441. [PubMed: 6837749]
- Ballatori N, and Clarkson TW 1984 Dependence of biliary secretion of inorganic mercury on the biliary transport of glutathione. *Biochem. Pharmacol* 33:1093–1098. [PubMed: 6712719]
- Ballatori N, and Clarkson TW 1985a Biliary secretion of glutathione and of glutathione-metal complexes. *Fundam. Appl. Toxicol* 5:816–831. [PubMed: 4065458]
- Ballatori N, and Clarkson TW 1985b Sulfobromophthalein inhibition of glutathione and methylmercury secretion into bile. *Am. J. Physiol* 248:G238–G245. [PubMed: 3970204]
- Ballatori N, and Dutczak WJ 1994 Identification and characterization of high and low affinity transport systems for reduced glutathione in liver cell canalicular membranes. *J. Biol. Chem* 269:19731–19737. [PubMed: 8051053]
- Ballatori N, Hammond CL, Cunningham JB, Krance SM, and Marchan R 2005 Molecular mechanisms of reduced glutathione transport: Role of the MRP/CFTR/ABCC and OATP/SLC21A families of membrane proteins. *Toxicol. Appl. Pharmacol* 204:238–255. [PubMed: 15845416]
- Ballatori N, and Truong AT 1995 Multiple canalicular transport mechanisms for glutathione S-conjugates. Transport on both ATP- and voltage-dependent carriers. *J. Biol. Chem* 270:3594–3601. [PubMed: 7876095]

- Ballatori N, Wang W, and Lieberman MW 1998 Accelerated methylmercury elimination in gamma-glutamyl transpeptidase-deficient mice. *Am. J. Pathol* 152:1049–1055. [PubMed: 9546365]
- Bayen S, Koroleva E, Lee HK, and Obbard JP 2005 Persistent organic pollutants and heavy metals in typical seafoods consumed in Singapore. *J. Toxicol. Environ. Health A* 68:151–166. [PubMed: 15762177]
- Berlin M, and Gibson S 1963 Renal uptake, excretion, and retention of mercury. I. A study in the rabbit during infusion of mercuric chloride. *Arch. Environ. Health* 6:617–625. [PubMed: 13970886]
- Berlin M, and Ullberg S 1963a Accumulation and retention of mercury in the mouse. I. An autoradiographic study after a single intravenous injection of mercuric chloride. *Arch. Environ. Health* 6:589–601. [PubMed: 13970883]
- Berlin M, and Ullberg S, 1963b Accumulation and retention of mercury in the mouse. II. An autoradiographic comparison of phenylmercuric acetate with inorganic mercury. *Arch. Environ. Health* 6:602–609. [PubMed: 13970884]
- Berlin M, and Ullberg S 1963c Accumulation and retention of mercury in the mouse. III. An autoradiographic comparison of methylmercuric dicyandiamide with inorganic mercury. *Arch. Environ. Health* 6:610–616. [PubMed: 13970885]
- Berndt WO, Baggett JM, Blacker A, and Houser M 1985 Renal glutathione and mercury uptake by kidney. *Fundam. Appl. Toxicol* 5:832–839. [PubMed: 4065459]
- Betz AL, and Goldstein GW 1978 Polarity of the blood–brain barrier: Neutral amino acid transport into isolated brain capillaries. *Science* 202:225–227. [PubMed: 211586]
- Bluhm RE, Breyer JA, Bobbitt RG, Welch LW, Wood AJ, and Branch RA 1992 Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers. Part II: Hyperchloraemia and genitourinary symptoms. *Hum. Exp. Toxicol* 11:211–215. [PubMed: 1352116]
- Bode BP 2001 Recent molecular advances in mammalian glutamine transport. *J. Nutr* 131:2475S–2485S; discussion 2486S–2477S. [PubMed: 11533296]
- Bridges CC, Bauch C, Verrey F, and Zalups RK 2004 Mercuric conjugates of cysteine are transported by the amino acid transporter system b0,+; implications of molecular mimicry. *J. Am. Soc. Nephrol* 15:663–673. [PubMed: 14978168]
- Bridges CC, Joshee L, and Zalups RK 2008a MRP2 and the DMPS- and DMSA-mediated elimination of mercury in TR- and control rats exposed to thiol S-conjugates of inorganic mercury. *Toxicol. Sci* 105:211–220. [PubMed: 18511429]
- Bridges CC, Joshee L, and Zalups RK 2008b Multidrug resistance proteins and the renal elimination of inorganic mercury mediated by 2,3-dimercaptopropane-1-sulfonic acid and meso-2,3-dimercaptosuccinic acid. *J. Pharmacol. Exp. Ther* 324:383–390. [PubMed: 17940195]
- Bridges CC, Joshee L, and Zalups RK 2009 Effect of DMPS and DMSA on the placental and fetal disposition of methylmercury. *Placenta* 30:800–805. [PubMed: 19615742]
- Bridges CC, and Zalups RK 2004 Homocysteine, system b0,+ and the renal epithelial transport and toxicity of inorganic mercury. *Am. J. Pathol* 165:1385–1394. [PubMed: 15466402]
- Bridges CC, and Zalups RK 2006 System b0,+ and the transport of thiol-S-conjugates of methylmercury. *J. Pharmacol. Exp. Ther* 319:948–956. [PubMed: 16926263]
- Buchler M, Konig J, Brom M, Kartenbeck J, Spring H, Horie T, and Keppler D 1996 cDNA cloning of the hepatocyte canalicular isoform of the multidrug resistance protein, cMrp, reveals a novel conjugate export pump deficient in hyperbilirubinemic mutant rats. *J. Biol. Chem* 271:15091–15098. [PubMed: 8662992]
- Burckhardt BC, Drinkuth B, Menzel C, Konig A, Steffgen J, Wright SH, and Burckhardt G 2002 The renal Na+-dependent dicarboxylate transporter, NaDC-3, translocates dimethyl- and disulfhydryl-compounds and contributes to renal heavy metal detoxification. *J. Am. Soc. Nephrol* 13:2628–2638. [PubMed: 12397032]
- Cannon VT, Barfuss DW, and Zalups RK 2000 Molecular homology and the luminal transport of Hg2+ in the renal proximal tubule. *J. Am. Soc. Nephrol* 11:394–402. [PubMed: 10703663]

- Cannon VT, Zalups RK, and Barfuss DW 2001 Amino acid transporters involved in luminal transport of mercuric conjugates of cysteine in rabbit proximal tubule. *J. Pharmacol. Exp. Ther* 298:780–789. [PubMed: 11454942]
- Canonne-Hergaux F, Gruenheid S, Ponka P, and Gros P 1999 Cellular and subcellular localization of the Nramp2 iron transporter in the intestinal brush border and regulation by dietary iron. *Blood* 93:4406–4417. [PubMed: 10361139]
- Carmignani M, Boscolo P, Artese L, Del Rosso G, Porcelli G, Felaco M, Volpe AR, and Giuliano G 1992 Renal mechanisms in the cardiovascular effects of chronic exposure to inorganic mercury in rats. *Br. J. Ind. Med* 49:226–232. [PubMed: 1571292]
- Cember H, Gallagher P, and Faulkner A 1968 Distribution of mercury among blood fractions and serum proteins. *Am. Ind. Hyg. Assoc. J* 29:233–237. [PubMed: 4173106]
- Cha SH, Sekine T, Kusuhashi H, Yu E, Kim JY, Kim DK, Sugiyama Y, Kanai Y, and Endou H 2000 Molecular cloning and characterization of multispecific organic anion transporter 4 expressed in the placenta. *J. Biol. Chem* 275:4507–4512. [PubMed: 10660625]
- Cherian MG, and Clarkson TW 1976 Biochemical changes in rat kidney on exposure to elemental mercury vapor: Effect on biosynthesis of metallothionein. *Chem. Biol. Interact* 12:109–120. [PubMed: 1248059]
- Chillaron J, Roca R, Valencia A, Zorzano A, and Palacin M 2001 Heteromeric amino acid transporters: biochemistry, genetics, and physiology. *Am. J. Physiol. Renal Physiol* 281:F995–F1018. [PubMed: 11704550]
- Clarkson TW 1993 Molecular and ionic mimicry of toxic metals. *Annu. Rev. Pharmacol. Toxicol* 33:545–571. [PubMed: 8494351]
- Clarkson TW, and Magos L 1966 Studies on the binding of mercury in tissue homogenates. *Biochem. J* 99:62–70. [PubMed: 5966262]
- Clarkson TW, and Magos L 2006 The toxicology of mercury and its chemical compounds. *Crit. Rev. Toxicol* 36:609–662. [PubMed: 16973445]
- Dalton TP, He L, Wang B, Miller ML, Jin L, Stringer KF, Chang X, Baxter CS, and Nebert DW 2005 Identification of mouse SLC39A8 as the transporter responsible for cadmium-induced toxicity in the testis. *Proc. Natl. Acad. Sci. USA* 102:3401–3406. [PubMed: 15722412]
- Danscher G, Horsted-Bindslev P, and Rungby J 1990 Traces of mercury in organs from primates with amalgam fillings. *Exp. Mol. Pathol* 52:291–299. [PubMed: 2115006]
- Dave MH, Schulz N, Zecevic M, Wagner CA, and Verrey F 2004 Expression of heteromeric amino acid transporters along the murine intestine. *J. Physiol* 558:597–610. [PubMed: 15155792]
- Davidson PW, Strain JJ, Myers GJ, Thurston SW, Bonham MP, Shamlaye CF, Stokes-Riner A, Wallace JM, Robson PJ, Duffy EM, Georger LA, Sloane-Reeves J, Cernichiari E, Canfield RL, Cox C, Huang LS, Janciuras J, and Clarkson TW 2008 Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy. *Neurotoxicology* 29:767–775. [PubMed: 18590763]
- de Ceaurriz J, and Ban M 1990 Role of gamma-glutamyltranspeptidase and betalyase in the nephrotoxicity of hexachloro-1,3-butadiene and methyl mercury in mice. *Toxicol. Lett* 50:249–256. [PubMed: 1689880]
- de Ceaurriz J, Payan JP, Morel G, and Brondeau MT 1994 Role of extracellular glutathione and gamma-glutamyltranspeptidase in the disposition and kidney toxicity of inorganic mercury in rats. *J. Appl. Toxicol* 14:201–206. [PubMed: 7916024]
- Deeley RG, Westlake C, and Cole SP 2006 Transmembrane transport of endo- and xenobiotics by mammalian ATP-binding cassette multidrug resistance proteins. *Physiol. Rev* 86:849–899. [PubMed: 16816140]
- Di Simplicio P, Gorelli M, Ciuffreda P, and Leonzio C 1990 The relationship between gamma-glutamyl transpeptidase and Hg levels in Se/Hg antagonism in mouse liver and kidney. *Pharmacol. Res* 22:515–526. [PubMed: 1976248]
- Diamond GL, Klotzbach JM, and Stewart JR 1988 Complexing activity of 2,3-dimercapto-1-propanesulfonate and its disulfide auto-oxidation product in rat kidney. *J. Pharmacol. Exp. Ther* 246:270–274. [PubMed: 3392658]

- Dietert RR, and Dietert JM 2008 Potential for early-life immune insult including developmental immunotoxicity in autism and autism spectrum disorders: Focus on critical windows of immune vulnerability. *J. Toxicol. Environ. Health B* 11:660–680.
- Dunn JD, and Clarkson TW 1980 Does mercury exhalation signal demethylation of methylmercury? *Health Phys.* 38:411–414. [PubMed: 7390825]
- Dutczak WJ, and Ballatori N 1992 Gamma-glutamyltransferase-dependent biliary-hepatic recycling of methyl mercury in the guinea pig. *J. Pharmacol. Exp. Ther* 262:619–623. [PubMed: 1354255]
- Dutczak WJ, and Ballatori N 1994 Transport of the glutathione–methylmercury complex across liver canalicular membranes on reduced glutathione carriers. *J. Biol. Chem* 269:9746–9751. [PubMed: 8144567]
- Dutczak WJ, Clarkson TW, and Ballatori N 1991 Biliary-hepatic recycling of a xenobiotic: gallbladder absorption of methyl mercury. *Am. J. Physiol* 260:G873–G880. [PubMed: 2058675]
- Endo T, Nakaya S, Kimura R, and Murata T 1984 Gastrointestinal absorption of inorganic mercuric compounds in vivo and in situ. *Toxicol. Appl. Pharmacol* 74:223–229. [PubMed: 6234682]
- Fernandez-Checa JC, Ookhtens M, and Kaplowitz N 1993 Selective induction by phenobarbital of the electrogenic transport of glutathione and organic anions in rat liver canalicular membrane vesicles. *J. Biol. Chem* 268:10836–10841. [PubMed: 8496149]
- Fernandez-Checa JC, Takikawa H, Horie T, Ookhtens M, and Kaplowitz N 1992 Canalicular transport of reduced glutathione in normal and mutant Eisai hyperbilirubinemic rats. *J. Biol. Chem* 267:1667–1673. [PubMed: 1730711]
- Ferrier B, Martin M, and Roch-Ramel F 1983 Effects of *p*-aminohippurate and pyrazinoate on the renal excretion of salicylate in the rat: A micropuncture study. *J. Pharmacol. Exp. Ther* 224:451–458. [PubMed: 6822966]
- Foulkes EC 1993 Metallothionein and glutathione as determinants of cellular retention and extrusion of cadmium and mercury. *Life Sci.* 52:1617–1620. [PubMed: 8483390]
- Foulkes EC 2000 Transport of toxic heavy metals across cell membranes. *Proc. Soc. Exp. Biol. Med* 223:234–240. [PubMed: 10719835]
- Foulkes EC, and Bergman D 1993 Inorganic mercury absorption in mature and immature rat jejunum: Transcellular and intercellular pathways in vivo and in everted sacs. *Toxicol. Appl. Pharmacol* 120:89–95. [PubMed: 8511785]
- Friberg L 1959 Studies on the metabolism of mercuric chloride and methyl mercury dicyandiamide; Experiments on rats given subcutaneous injections with radioactive mercury Hg²⁰³. *AMA Arch. Ind. Health* 20:42–49. [PubMed: 13660519]
- Friberg L, Odeblad E, and Forssman S 1957 Distribution of two mercury compounds in rabbits after a single subcutaneous injection; a radiometric and autoradiographic study of the distribution of mercuric chloride and phenylmercuric acetate. *AMA Arch. Ind. Health* 16:163–168. [PubMed: 13443532]
- Friedman HL 1957 Relationship between chemical structure and biological activity in mercurial compounds. *Ann. N Y Acad. Sci* 65:461–470. [PubMed: 13411944]
- Fuhr BJ, and Rabenstein DL 1973 Nuclear magnetic resonance studies of the solution chemistry of metal complexes. IX. The binding of cadmium, zinc, lead, and mercury by glutathione. *J. Am. Chem. Soc* 95:6944–6950. [PubMed: 4784285]
- Gage JC 1964 Distribution and excretion of methyl and phenyl mercury salts. *Br. J. Ind. Med* 21:197–202. [PubMed: 14180477]
- Ganapathy V, Ganapathy ME, and Leibach FH 2001 *Intestinal transport of peptides and amino acids*. New York: Academic Press.
- Garcia-Ruiz C, Fernandez-Checa JC, and Kaplowitz N 1992 Bidirectional mechanism of plasma membrane transport of reduced glutathione in intact rat hepatocytes and membrane vesicles. *J. Biol. Chem* 267:22256–22264. [PubMed: 1429578]
- Geier DA, and Geier MR 2007 A prospective study of mercury toxicity biomarkers in autistic spectrum disorders. *J. Toxicol. Environ. Health A* 70:1723–1730. [PubMed: 17885929]
- Gonska T, Hirsch JR, and Schlatter E 2000 Amino acid transport in the renal proximal tubule. *Amino Acids* 19:395–407. [PubMed: 11128548]

- Gregus Z, Stein AF, and Klaassen CD 1987 Effect of inhibition of gamma-glutamyltranspeptidase on biliary and urinary excretion of glutathione-derived thiols and methylmercury. *J. Pharmacol. Exp. Ther* 242:27–32. [PubMed: 2886637]
- Hahn LJ, Kloiber R, Leininger RW, Vimy MJ, and Lorscheider FL 1990 Whole-body imaging of the distribution of mercury released from dental fillings into monkey tissues. *FASEB J.* 4:3256–3260. [PubMed: 2227216]
- Hahn LJ, Kloiber R, Vimy MJ, Takahashi Y, and Lorscheider FL 1989 Dental “silver” tooth fillings: A source of mercury exposure revealed by whole-body image scan and tissue analysis. *FASEB J.* 3:2641–2646. [PubMed: 2636872]
- Harada M 1978 Congenital Minamata disease: Intrauterine methylmercury poisoning. *Teratology* 18:285–288. [PubMed: 362594]
- Harada M 1995 Minamata disease: Methylmercury poisoning in Japan caused by environmental pollution. *Crit. Rev. Toxicol* 25:1–24. [PubMed: 7734058]
- He L, Girijashanker K, Dalton TP, Reed J, Li H, Soleimani M, and Nebert DW 2006 ZIP8, member of the solute-carrier-39 SLC39 metal-transporter family: Characterization of transporter properties. *Mol. Pharmacol* 70:171–180. [PubMed: 16638970]
- Hilgendorf C, Ahlin G, Seithel A, Artursson P, Ungell AL, and Karlsson J 2007 Expression of thirty-six drug transporter genes in human intestine, liver, kidney, and organotypic cell lines. *Drug Metab. Dispos* 35:1333–1340. [PubMed: 17496207]
- Hirayama K 1975 Transport mechanism of methyl mercury. Intestinal absorption, biliary excretion and distribution of methyl mercury. *Kumamoto Med. J* 28:151–163. [PubMed: 1223551]
- Hirayama K 1980 Effect of amino acids on brain uptake of methyl mercury. *Toxicol. Appl. Pharmacol* 55:318–323. [PubMed: 7423520]
- Hirayama K 1985 Effects of combined administration of thiol compounds and methylmercury chloride on mercury distribution in rats. *Biochem. Pharmacol* 34:2030–2032. [PubMed: 4004919]
- Hoyle I, and Handy RD 2005 Dose-dependent inorganic mercury absorption by isolated perfused intestine of rainbow trout, *Oncorhynchus mykiss*, involves both amiloride-sensitive and energy-dependent pathways. *Aquat. Toxicol* 72:147–159. [PubMed: 15748753]
- Hughes WL 1957 A physicochemical rationale for the biological activity of mercury and its compounds. *Ann. NY Acad. Sci* 65:454–460. [PubMed: 13411943]
- Hultman P, Bell LJ, Enestrom S, and Pollard KM 1992 Murine susceptibility to mercury. I. Autoantibody profiles and systemic immune deposits in inbred, congenic, and intra-H-2 recombinant strains. *Clin. Immunol. Immunopathol* 65:98–109. [PubMed: 1395135]
- Hultman P, and Enestrom S 1986 Localization of mercury in the kidney during experimental acute tubular necrosis studied by the cytochemical silver amplification method. *Br. J. Exp. Pathol* 67:493–503. [PubMed: 3741775]
- Hultman P, and Enestrom S 1992 Dose-response studies in murine mercury-induced autoimmunity and immune-complex disease. *Toxicol. Appl. Pharmacol* 113:199–208. [PubMed: 1532866]
- Hultman P, Enestrom S, and von Schenck H 1985 Renal handling of inorganic mercury in mice. The early excretion phase following a single intravenous injection of mercuric chloride studied by the silver amplification method. *Virchows Arch. B Cell. Pathol. Incl. Mol. Pathol* 49:209–224. [PubMed: 2865844]
- Iioka H, Moriyama I, Oku M, Hino K, Itani Y, Okamura Y, and Ichijo M 1987 [The effect of inorganic mercury on placental amino acid transport using microvillous membrane vesicles]. *Nippon Sanka Fujinka Gakkai Zasshi* 39:202–206. [PubMed: 3102650]
- Ilback NG, Frisk P, Tallkvist J, Gadhasson IL, Blomberg J, and Friman G 2008 Gastrointestinal uptake of trace elements are changed during the course of a common human viral Coxsackievirus B3 infection in mice. *J. Trace Elem. Med. Biol* 22:120–130. [PubMed: 18565424]
- Inouye M, and Kajiwar Y 1988 Developmental disturbances of the fetal brain in guinea-pigs caused by methylmercury. *Arch. Toxicol* 62:15–21. [PubMed: 3190452]
- Inouye M, and Kajiwar Y 1990 Strain difference of the mouse in manifestation of hydrocephalus following prenatal methylmercury exposure. *Teratology* 41:205–210. [PubMed: 2321164]
- Inouye M, Murao K, and Kajiwar Y 1985 Behavioral and neuropathological effects of prenatal methylmercury exposure in mice. *Neurobehav. Toxicol. Teratol* 7:227–232. [PubMed: 4033863]

- Islinger F, Gekle M, and Wright SH 2001 Interaction of 2,3-dimercapto-1-propane sulfonate with the human organic anion transporter hOAT1. *J. Pharmacol. Exp. Ther* 299:741–747. [PubMed: 11602689]
- Itagaki S, Chiba M, Kobayashi M, Hirano T, and Iseki K 2008 Contribution of multidrug resistance-associated protein 2 to secretory intestinal transport of organic anions. *Biol. Pharm. Bull* 31:146–148. [PubMed: 18175959]
- Jaffe KM, Shurtleff DB, and Robertson WO 1983 Survival after acute mercury vapor poisoning. *Am. J. Dis. Child* 137:749–751. [PubMed: 6869332]
- Jansson T 2001 Amino acid transporters in the human placenta. *Pediatr. Res* 49:141–147. [PubMed: 11158505]
- Jernelov AA 1973 A new biochemical pathway for the methylation of mercury and some ecological implications. Springfield, IL: Thomas.
- Joshi JG, Szczekani SR, and Fleming JT 1989 Ferritin—A general metal detoxicant. *Biol. Trace Elem. Res* 21:105–110. [PubMed: 2484575]
- Jung SM, Lee WK, Kwak JO, Jung SY, Park J, Kim WY, Kim J, and Cha SH 2006 Identification of a novel murine organic anion transporter like protein 1 OATLP1 expressed in the kidney. *Exp. Mol. Med* 38:485–493. [PubMed: 17079864]
- Kajiwaru Y, and Inouye M 1986 Effects of methylmercury and mercuric chloride on preimplantation mouse embryos in vivo. *Teratology* 33:231–237. [PubMed: 3738818]
- Kajiwaru Y, and Inouye M 1992 Inhibition of implantation caused by methylmercury and mercuric chloride in mouse embryos in vivo. *Bull. Environ. Contam. Toxicol* 49:541–546. [PubMed: 1421848]
- Kajiwaru Y, Yasutake A, Adachi T, and Hirayama K 1996 Methylmercury transport across the placenta via neutral amino acid carrier. *Arch. Toxicol* 70:310–314. [PubMed: 8852703]
- Keppler D, and König J 1997 Hepatic canalicular membrane 5: Expression and localization of the conjugate export pump encoded by the MRP2 cMRP/cMOAT gene in liver. *FASEB J.* 11:509–516. [PubMed: 9212074]
- Kern JK, and Jones AM 2006 Evidence of toxicity, oxidative stress, and neuronal insult in autism. *J. Toxicol. Environ. Health B* 9:485–499.
- Kerper LE, Ballatori N, and Clarkson TW 1992 Methylmercury transport across the blood-brain barrier by an amino acid carrier. *Am. J. Physiol* 262:R761–R765. [PubMed: 1590471]
- Kitamura Y, Kusuhashi H, and Sugiyama Y 2009 Functional characterization of multidrug resistance-associated protein 3 Mrp3/Abcc3 in the basolateral efflux of glucuronide conjugates in the mouse small intestine. *J. Pharmacol. Exp. Ther* Epub ahead of print: PMID: 19889793.
- Koh AS, Simmons-Willis TA, Pritchard JB, Grassl SM, and Ballatori N 2002 Identification of a mechanism by which the methylmercury antidotes N-acetylcysteine and dimercaptopropanesulfonate enhance urinary metal excretion: Transport by the renal organic anion transporter-1. *Mol. Pharmacol* 62:921–926. [PubMed: 12237339]
- Kojima R, Sekine T, Kawachi M, Cha SH, Suzuki Y, and Endou H 2002 Immunolocalization of multispecific organic anion transporters, OAT1, OAT2, and OAT3, in rat kidney. *J. Am. Soc. Nephrol* 13:848–857. [PubMed: 11912243]
- Kudo Y, and Boyd CA 2002 Human placental amino acid transporter genes: Expression and function. *Reproduction* 124:593–600. [PubMed: 12416997]
- Landner L 1971 Biochemical model for the biological methylation of mercury suggested from methylation studies in vivo with *Neurospora crassa*. *Nature* 230:452–454. [PubMed: 4929974]
- Laporte JM, Andres S, and Mason RP 2002 Effect of ligands and other metals on the uptake of mercury and methylmercury across the gills and the intestine of the blue crab *Callinectes sapidus*. *Comp. Biochem. Physiol. C Toxicol Pharmacol* 131:185–196. [PubMed: 11879786]
- Lau S, and Sarkar B 1979 Inorganic mercury(II)-binding components in normal human blood serum. *J. Toxicol. Environ. Health* 5:907–916. [PubMed: 513155]
- Leaner JJ, and Mason RP 2002 Methylmercury accumulation and fluxes across the intestine of channel catfish, *Ictalurus punctatus*. *Comp. Biochem. Physiol. C Toxicol. Pharmacol* 132:247–259. [PubMed: 12106901]

- Leazer TM, and Klaassen CD 2003 The presence of xenobiotic transporters in rat placenta. *Drug Metab. Dispos* 31:153–167. [PubMed: 12527696]
- Leslie EM, Deeley RG, and Cole SP 2005 Multidrug resistance proteins: Role of P-glycoprotein, MRP1, MRP2, and BCRP ABCG2 in tissue defense. *Toxicol. Appl. Pharmacol* 204:216–237. [PubMed: 15845415]
- Lin JL, and Lim PS 1993 Massive oral ingestion of elemental mercury. *J. Toxicol. Clin. Toxicol* 31:487–492. [PubMed: 8355325]
- Liu Z, Li H, Soleimani M, Girijashanker K, Reed JM, He L, Dalton TP, and Nebert DW 2008 Cd^{2+} versus Zn^{2+} uptake by the ZIP8 HCO_3^- -dependent symporter: Kinetics, electrogenicity and trafficking. *Biochem. Biophys. Res. Commun* 365:814–820. *J. Ind. Hyg. Toxicol.* 31:190–200. [PubMed: 18037372]
- Madejczyk MS, Aremu DA, Simmons-Willis TA, Clarkson TW, and Ballatori N 2007 Accelerated urinary excretion of methylmercury following administration of its antidote *N*-acetylcysteine requires Mrp2/Abcc2, the apical multidrug resistance-associated protein. *J. Pharmacol. Exp. Ther* 322:378–384. [PubMed: 17429056]
- Magos L, and Butler WH 1976 The kinetics of methylmercury administered repeatedly to rats. *Arch. Toxicol* 35:25–39. [PubMed: 946405]
- Magos L, Brown AW, Sparrow S, Bailey E, Snowden RT, and Skipp WR 1985 The comparative toxicology of ethyl- and methylmercury. *Arch. Toxicol* 57:260–267. [PubMed: 4091651]
- Magos L, Clarkson TW, and Allen J 1978 The interrelationship between non-protein bound thiols and the biliary excretion of methylmercury. *Biochem. Pharmacol* 27:2203–2208. [PubMed: 728172]
- Magos L, Peristianis GC, Clarkson TW, Brown A, Preston S, and Snowden RT 1981 Comparative study of the sensitivity of male and female rats to methylmercury. *Arch. Toxicol* 48:11–20. [PubMed: 7283745]
- Maher JM, Slitt AL, Cherrington NJ, Cheng X, and Klaassen CD 2005 Tissue distribution and hepatic and renal ontogeny of the multidrug resistance-associated protein Mrp family in mice. *Drug Metab. Dispos* 33:947–955. [PubMed: 15802388]
- Matsumoto H, Koya G, and Takeuchi T 1965 Fetal Minamata disease. A neuropathological study of two cases of intrauterine intoxication by a methyl mercury compound. *J. Neuropathol. Exp. Neurol* 24:563–574. [PubMed: 5890913]
- McNeil SI, Bhatnagar MK, and Turner CJ 1988 Combined toxicity of ethanol and methylmercury in rat. *Toxicology* 53:345–363. [PubMed: 3212792]
- Mokrzan EM, Kerper LE, Ballatori N, and Clarkson TW 1995 Methylmercury-thiol uptake into cultured brain capillary endothelial cells on amino acid system L. *J. Pharmacol. Exp. Ther* 272:1277–1284. [PubMed: 7891344]
- Motohashi H, Sakurai Y, Saito H, Masuda S, Urakami Y, Goto M, Fukatsu A, Ogawa O, and Inui K 2002 Gene expression levels and immunolocalization of organic ion transporters in the human kidney. *J. Am. Soc. Nephrol* 13:866–874. [PubMed: 11912245]
- Mulder KM, and Kostyniak PJ 1985 Effect of L-alpha *S,S*-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid on urinary excretion of methylmercury in the mouse. *J. Pharmacol. Exp. Ther* 234:156–160. [PubMed: 4009498]
- Murphy MJ, Culliford EJ, and Parsons V 1979 A case of poisoning with mercuric chloride. *Resuscitation* 7:35–44. [PubMed: 493732]
- Mussini E 1958 [Distribution in the organism & diuretic activity of p-chlorobenzoic acid mercury salt.]. *Boll. Soc. Ital. Biol. Sper* 34:1586–1588. [PubMed: 13607870]
- Naganuma A, Oda-Urano N, Tanaka T, and Imura N 1988 Possible role of hepatic glutathione in transport of methylmercury into mouse kidney. *Biochem. Pharmacol* 37:291–296. [PubMed: 3342085]
- Nakanishi T, Hatanaka T, Huang W, Prasad PD, Leibach FH, Ganapathy ME, and Ganapathy V 2001 Na^+ - and Cl^- -coupled active transport of carnitine by the amino acid transporter $\text{ATB}^{0,+}$ from mouse colon expressed in HRPE cells and *Xenopus* oocytes. *J. Physiol* 532:297–304. [PubMed: 11306651]

- Norseth T, and Clarkson TW 1970a Biotransformation of methylmercury salts in the rat studied by specific determination of inorganic mercury. *Biochem. Pharmacol* 19:2775–2783. [PubMed: 5478586]
- Norseth T, and Clarkson TW 1970b Studies on the biotransformation of ^{203}Hg -labeled methyl mercury chloride in rats. *Arch. Environ. Health* 21:717–727. [PubMed: 5478557]
- Norseth T, and Clarkson TW 1971 Intestinal transport of ^{203}Hg -labeled methyl mercury chloride. Role of biotransformation in rats. *Arch. Environ. Health* 22:568–577. [PubMed: 5550173]
- Oka JA, Christensen MD, and Weigel PH 1989 Hyperosmolarity inhibits galactosyl receptor-mediated but not fluid phase endocytosis in isolated rat hepatocytes. *J. Biol. Chem* 264:12016–12024. [PubMed: 2545695]
- Oldendorf WH 1973 Stereospecificity of blood–brain barrier permeability to amino acids. *Am. J. Physiol* 224:967–969. [PubMed: 4698813]
- Omata S, Sakimura K, Ishii T, and Sugano H 1978 Chemical nature of a methylmercury complex with a low molecular weight in the liver cytosol of rats exposed to methylmercury chloride. *Biochem. Pharmacol* 27:1700–1702. [PubMed: 697910]
- Omata S, Sato M, Sakimura K, and Sugano H 1980 Time-dependent accumulation of inorganic mercury in subcellular fractions of kidney, liver, and brain of rats exposed to methylmercury. *Arch. Toxicol* 44:231–241. [PubMed: 7396710]
- Palacin M, Estevez R, Bertran J, and Zorzano A 1998 Molecular biology of mammalian plasma membrane amino acid transporters. *Physiol. Rev* 78:969–1054. [PubMed: 9790568]
- Palacin M, Fernandez E, Chillaron J, and Zorzano A 2001 The amino acid transport system $\text{b}^{0,+}$ and cystinuria. *Mol. Membr. Biol* 18:21–26. [PubMed: 11396607]
- Planas-Bohne F 1981 The effect of 2,3-dimercaptopropane-1-sulfonate and dimercaptosuccinic acid on the distribution and excretion of mercuric chloride in rats. *Toxicology* 19:275–278. [PubMed: 6262950]
- Prickett CS, Laug EP, and Kunze FM 1950 Distribution of mercury in rats following oral and intravenous administration of mercuric acetate and phenylmercuric acetate. *Proc. Soc. Exp. Biol. Med* 73:585–588. [PubMed: 15417605]
- Prime-Chapman HM, Fearn RA, Cooper AE, Moore V, and Hirst BH 2004 Differential multidrug resistance-associated protein 1 through 6 isoform expression and function in human intestinal epithelial Caco-2 cells. *J. Pharmacol. Exp. Ther* 311:476–484. [PubMed: 15210835]
- Pritchard JB 1988 Coupled transport of -aminohippurate by rat kidney basolateral membrane vesicles. *Am. J. Physiol* 255:F597–F604. [PubMed: 3177651]
- Refsvik T 1978 Excretion of methyl mercury in rat bile: The effect of diethylmaleate, cyclohexene oxide and acrylamide. *Acta Pharmacol. Toxicol. Copenh* 42:135–141. [PubMed: 580156]
- Refsvik T 1982 Excretion of methyl mercury in rat bile: The effect of thioctic acid, thionalide, hexadecyl- and octadecylmercaptoacetate. *Acta Pharmacol. Toxicol. Copenh* 50:196–205. [PubMed: 6807055]
- Refsvik T, and Norseth T 1975 Methyl mercuric compounds in rat bile. *Acta Pharmacol. Toxicol. Copenh* 36:67–78. [PubMed: 1173724]
- Richardson RJ, and Murphy SD 1975 Effect of glutathione depletion on tissue deposition of methylmercury in rats. *Toxicol. Appl. Pharmacol* 31:505–519. [PubMed: 1145635]
- Risher JF, and De Rosa CT 2007 Inorganic: The other mercury. *J. Environ. Health* 70:9–16; discussion 40.
- Rodier PM, Kates B, and Simons R 1988 Mercury localization in mouse kidney over time: Autoradiography versus silver staining. *Toxicol. Appl. Pharmacol* 92:235–245. [PubMed: 2448914]
- Rooney JP 2007 The role of thiols, dithiols, nutritional factors and interacting ligands in the toxicology of mercury. *Toxicology* 234:145–156. [PubMed: 17408840]
- Rost D, Mahner S, Sugiyama Y, and Stremmel W 2002 Expression and localization of the multidrug resistance-associated protein 3 in rat small and large intestine. *Am. J. Physiol. Gastrointest Liver Physiol* 282:G720–G726. [PubMed: 11897632]

- Rowens B, Guerrero-Betancourt D, Gottlieb CA, Boyes RJ, and Eichenhorn MS 1991 Respiratory failure and death following acute inhalation of mercury vapor. A clinical and histologic perspective. *Chest* 99:185–190. [PubMed: 1984951]
- Rubino FM, Verduci C, Giampiccolo R, Pulvirenti S, Brambilla G, and Colombi A 2004 Molecular characterization of homo- and heterodimeric mercury(II)-bis-thiolates of some biologically relevant thiols by electrospray ionization and triple quadrupole tandem mass spectrometry. *J. Am. Soc. Mass Spectrom* 15:288–300. [PubMed: 14998531]
- Ruprecht J 2008 Dimaval: Scientific product monograph. Berlin, Germany: Heyl Pharmaceuticals.
- Samuels ER, Heick HM, McLaine PN, and Farant JP 1982 A case of accidental inorganic mercury poisoning. *J. Anal. Toxicol* 6:120–122. [PubMed: 7109552]
- Schaub TP, Kartenbeck J, König J, Spring H, Dorsam J, Staehler G, Storkel S, Thon WF, and Keppler D 1999 Expression of the MRP2 gene-encoded conjugate export pump in human kidney proximal tubules and in renal cell carcinoma. *J. Am. Soc. Nephrol* 10:1159–1169. [PubMed: 10361853]
- Schaub TP, Kartenbeck J, König J, Vogel O, Witzgall R, Kriz W, and Keppler D 1997 Expression of the conjugate export pump encoded by the *mrp2* gene in the apical membrane of kidney proximal tubules. *J. Am. Soc. Nephrol* 8:1213–1221. [PubMed: 9259347]
- Shimomura A, Chonko AM, and Grantham JJ 1981 Basis for heterogeneity of *para*-aminohippurate secretion in rabbit proximal tubules. *Am. J. Physiol* 240:F430–F436. [PubMed: 7235017]
- Shoji T, Suzuki H, Kusuhara H, Watanabe Y, Sakamoto S, and Sugiyama Y 2004 ATP-dependent transport of organic anions into isolated basolateral membrane vesicles from rat intestine. *Am. J. Physiol. Gastrointest. Liver Physiol* 287:G749–G756. [PubMed: 15217779]
- Simmonds MP, Haraguchi K, Endo T, Cipriano F, Palumbi SR, and Troisi GM 2002 Human health significance of organochlorine and mercury contaminants in Japanese whale meat. *J. Toxicol. Environ. Health A* 65:1211–1235. [PubMed: 12167206]
- Simmons-Willis TA, Koh AS, Clarkson TW, and Ballatori N 2002 Transport of a neurotoxicant by molecular mimicry: The methyl mercury-L-cysteine complex is a substrate for human L-type large neutral amino acid transporter LAT 1 and LAT2. *Biochem. J* 367:239–246. [PubMed: 12117417]
- Sloan JL, and Mager S 1999 Cloning and functional expression of a human Na⁺ and Cl[−]-dependent neutral and cationic amino acid transporter B⁰⁺. *J. Biol. Chem* 274:23740–23745. [PubMed: 10446133]
- Soni JP, Singhania RU, Bansal A, and Rathi G 1992 Acute mercury vapor poisoning. *Indian Pediatr* 29:365–368. [PubMed: 1612685]
- St-Pierre MV, Serrano MA, Macias RI, Dubs U, Hoechli M, Lauper U, Meier PJ, and Marin JJ 2000 Expression of members of the multidrug resistance protein family in human term placenta. *Am. J. Physiol. Regul. Integr. Comp. Physiol* 279:R1495–R1503. [PubMed: 11004020]
- Sugawara N, Lai YR, Sugawara C, and Arizono K 1998 Decreased hepatobiliary secretion of inorganic mercury, its deposition and toxicity in the Eisai hyperbilirubinemic rat with no hepatic canalicular organic anion transporter. *Toxicology* 126:23–31. [PubMed: 9585089]
- Swensson A, and Ulfvarson U 1968 Distribution and excretion of various mercury compounds after single injections in poultry. *Acta Pharmacol. Toxicol. Copenh* 26:259–272. [PubMed: 5695825]
- Tanaka-Kagawa T, Naganuma A, and Imura N 1993 Tubular secretion and reabsorption of mercury compounds in mouse kidney. *J. Pharmacol. Exp. Ther* 264:776–782. [PubMed: 8094752]
- Tanaka T, Naganuma A, and Imura N 1990 Role of gamma-glutamyltranspeptidase in renal uptake and toxicity of inorganic mercury in mice. *Toxicology* 60:187–198. [PubMed: 1969183]
- Tanaka T, Naganuma A, Kobayashi K, and Imura N 1991 An explanation for strain and sex differences in renal uptake of methylmercury in mice. *Toxicology* 69:317–329. [PubMed: 1683032]
- Tanaka T, Naganuma A, Miura N, and Imura N 1992 Role of testosterone in gamma-glutamyltranspeptidase-dependent renal methylmercury uptake in mice. *Toxicol. Appl. Pharmacol* 112:58–63. [PubMed: 1346343]
- Taugner R 1966 [On the renal uptake and intrarenal distribution of sublimate and Hg-cysteine]. *Arzneimittelforschung* 16:1120–1121. [PubMed: 6014905]

- Taugner R, Winkel K, and Iravani J 1966 [On the localization of mercuric chloride concentration in the rat kidney]. *Virchows Arch. Pathol. Anat. Physiol. Klin. Med* 340:369–383. [PubMed: 5299377]
- Terlouw SA, Graeff C, Smeets PH, Fricker G, Russel FG, Masereeuw R, and Miller DS 2002 Short- and long-term influences of heavy metals on anionic drug efflux from renal proximal tubule. *J. Pharmacol. Exp. Ther* 301:578–585. [PubMed: 11961059]
- Thomas DJ, and Smith JC 1979 Partial characterization of a low-molecular-weight methylmercury complex in rat cerebrum. *Toxicol. Appl. Pharmacol* 47:547–556. [PubMed: 442094]
- Thomas DJ, and Smith JC 1982 Effects of coadministered low-molecular-weight thiol compounds on short-term distribution of methyl mercury in the rat. *Toxicol. Appl. Pharmacol* 62:104–110. [PubMed: 7064146]
- Ullrich KJ, Rumrich G, Fritzsch G, and Kloss S 1987 Contraluminal para-aminohippurate PAH transport in the proximal tubule of the rat kidney. II. Specificity: Aliphatic dicarboxylic acids. *Pflugers Arch.* 408:38–45. [PubMed: 3822770]
- Urano T, Iwasaki A, Himeno S, Naganuma A, and Imura N 1990 Absorption of methylmercury compounds from rat intestine. *Toxicol. Lett* 50:159–164. [PubMed: 2309235]
- Wagner CA, Lang F, and Broer S 2001 Function and structure of heterodimeric amino acid transporters. *Am. J. Physiol. Cell Physiol* 281:C1077–C1093. [PubMed: 11546643]
- Wakita Y 1987 Hypertension induced by methyl mercury in rats. *Toxicol. Appl. Pharmacol* 89:144–147. [PubMed: 3590186]
- Wang W, Clarkson TW, and Ballatori N 2000 Gamma-glutamyl transpeptidase and l-cysteine regulate methylmercury uptake by HepG2 cells, a human hepatoma cell line. *Toxicol. Appl. Pharmacol* 168:72–78. [PubMed: 11000102]
- Warkany J, and Hubbard DM 1953 A crodynia and mercury. *J. Pediatr* 42:365–386. [PubMed: 13035637]
- Wei H, Qiu L, Divine KK, Ashbaugh MD, McIntyre LC Jr., Fernando Q, and Gandolfi AJ 1999 Toxicity and transport of three synthesized mercury–thiol complexes in isolated rabbit renal proximal tubule suspensions. *Drug Chem Toxicol* 22:323–341. [PubMed: 10234470]
- World Health Organization. 2007 Mercury.
- Wu G 1995 Screening of potential transport systems for methyl mercury uptake in rat erythrocytes at 5 degrees by use of inhibitors and substrates. *Pharmacol Toxicol* 77:169–176. [PubMed: 8884879]
- Wu G 1996 Methylmercury-cysteine uptake by rat erythrocytes: Evidence for several transport systems. *J. Appl. Toxicol* 16:77–83. [PubMed: 8821680]
- Wu G 1997 Effect of probenecid on the transport of methyl mercury in erythrocytes by the organic anion transport system. *Arch. Toxicol* 71:218–222. [PubMed: 9101037]
- Yasutake A, Hirayama K, and Inoue M 1989 Mechanism of urinary excretion of methylmercury in mice. *Arch. Toxicol* 63:479–483. [PubMed: 2575893]
- Yokooji T, Murakami T, Yumoto R, Nagai J, and Takano M 2007 Site-specific bidirectional efflux of 2,4-dinitrophenyl-S-glutathione, a substrate of multidrug resistance-associated proteins, in rat intestine and Caco-2 cells. *J. Pharm. Pharmacol* 59:513–520. [PubMed: 17430634]
- Zalups RK 1991a Autometallographic localization of inorganic mercury in the kidneys of rats: Effect of unilateral nephrectomy and compensatory renal growth. *Exp. Mol. Pathol* 54:10–21. [PubMed: 1995316]
- Zalups RK 1991b Method for studying the in vivo accumulation of inorganic mercury in segments of the nephron in the kidneys of rats treated with mercuric chloride. *J. Pharmacol. Methods* 26:89–104. [PubMed: 1943126]
- Zalups RK 1991c Renal accumulation and intrarenal distribution of inorganic mercury in the rabbit: effect of unilateral nephrectomy and dose of mercuric chloride. *J. Toxicol. Environ. Health* 33:213–228. [PubMed: 2051495]
- Zalups RK 1993a Early aspects of the intrarenal distribution of mercury after the intravenous administration of mercuric chloride. *Toxicology* 79:215–228. [PubMed: 8316951]
- Zalups RK 1993b Influence of 2,3-dimercaptopropane-1-sulfonate DMPS and *meso*-2,3-dimercaptosuccinic acid DMSA on the renal disposition of mercury in normal and uninephrectomized rats exposed to inorganic mercury. *J. Pharmacol. Exp. Ther* 267:791–800. [PubMed: 8246154]

- Zalups RK 1995 Organic anion transport and action of gamma-glutamyl transpeptidase in kidney linked mechanistically to renal tubular uptake of inorganic mercury. *Toxicol. Appl. Pharmacol* 132:289–298. [PubMed: 7785056]
- Zalups RK 1997 Enhanced renal outer medullary uptake of mercury associated with uninephrectomy: implication of a luminal mechanism. *J. Toxicol. Environ. Health* 50:173–194. [PubMed: 9048960]
- Zalups RK 1998a Basolateral uptake of inorganic mercury in the kidney. *Toxicol. Appl. Pharmacol* 151:192–199. [PubMed: 9705903]
- Zalups RK 1998b Basolateral uptake of mercuric conjugates of *N*-acetylcysteine and cysteine in the kidney involves the organic anion transport system. *J. Toxicol. Environ. Health A* 55:13–29. [PubMed: 9747601]
- Zalups RK 1998c Intestinal handling of mercury in the rat: implications of intestinal secretion of inorganic mercury following biliary ligation or cannulation. *J. Toxicol. Environ. Health A* 53:615–636. [PubMed: 9572160]
- Zalups RK 2000 Molecular interactions with mercury in the kidney. *Pharmacol. Rev* 52:113–143. [PubMed: 10699157]
- Zalups RK, and Ahmad S 2004 Homocysteine and the renal epithelial transport and toxicity of inorganic mercury: Role of basolateral transporter organic anion transporter 1. *J. Am. Soc. Nephrol* 15:2023–2031. [PubMed: 15284288]
- Zalups RK, and Ahmad S 2005a Handling of cysteine S-conjugates of methylmercury in MDCK cells expressing human OAT1. *Kidney Int* 68:1684–1699. [PubMed: 16164645]
- Zalups RK, and Ahmad S 2005b Handling of the homocysteine S-conjugate of methylmercury by renal epithelial cells: Role of organic anion transporter 1 and amino acid transporters. *J. Pharmacol. Exp. Ther* 315:896–904. [PubMed: 16081680]
- Zalups RK, and Ahmad S 2005c Transport of *N*-acetylcysteine s-conjugates of methylmercury in Madin-Darby canine kidney cells stably transfected with human isoform of organic anion transporter 1. *J. Pharmacol. Exp. Ther* 314:1158–1168. [PubMed: 15908511]
- Zalups RK, Aslamkhan AG, and Ahmad S 2004 Human organic anion transporter 1 mediates cellular uptake of cysteine-S conjugates of inorganic mercury. *Kidney Int.* 66:251–261. [PubMed: 15200431]
- Zalups RK, and Barfuss D 1990 Accumulation of inorganic mercury along the renal proximal tubule of the rabbit. *Toxicol. Appl. Pharmacol* 106:245–253. [PubMed: 2256114]
- Zalups RK, and Barfuss D 1993 Transport and toxicity of methylmercury along the proximal tubule of the rabbit. *Toxicol. Appl. Pharmacol* 121:176–185. [PubMed: 8346534]
- Zalups RK, and Barfuss D 1995 Pretreatment with *p*-aminohippurate inhibits the renal uptake and accumulation of injected inorganic mercury in the rat. *Toxicology* 103:23–35. [PubMed: 8525487]
- Zalups RK, and Barfuss D 1998a Participation of mercuric conjugates of cysteine, homocysteine, and *N*-acetylcysteine in mechanisms involved in the renal tubular uptake of inorganic mercury. *J. Am. Soc. Nephrol* 9:551–561. [PubMed: 9555656]
- Zalups RK, and Barfuss D 1998b Small aliphatic dicarboxylic acids inhibit renal uptake of administered mercury. *Toxicol. Appl. Pharmacol* 148:183–193. [PubMed: 9465278]
- Zalups RK, Barfuss DW, and Lash LH 1999a Disposition of inorganic mercury following biliary obstruction and chemically induced glutathione depletion: Dispositional changes one hour after the intravenous administration of mercuric chloride. *Toxicol. Appl. Pharmacol* 154:135–144. [PubMed: 9925797]
- Zalups RK, Barfuss DW, and Lash LH 1999b Relationships between alterations in glutathione metabolism and the disposition of inorganic mercury in rats: Effects of biliary ligation and chemically induced modulation of glutathione status. *Chem. Biol. Interact* 123:171–195. [PubMed: 10654838]
- Zalups RK, and Bridges CC 2009 MRP2 involvement in renal proximal tubular elimination of methylmercury mediated by DMPS or DMSA. *Toxicol. Appl. Pharmacol* 235:10–17. [PubMed: 19063911]

- Zalups RK and Diamond GL 1987a Intrarenal distribution of mercury in the rat: Effect of administered dose of mercuric chloride. *Bull. Environ. Contam. Toxicol* 38:67–72. [PubMed: 3814853]
- Zalups RK and Diamond GL 1987b Mercuric chloride-induced nephrotoxicity in the rat following unilateral nephrectomy and compensatory renal growth. *Virchows Arch. B Cell. Pathol. Incl. Mol. Pathol* 53:336–346. [PubMed: 2891217]
- Zalups RK, and Lash LH 1994 Advances in understanding the renal transport and toxicity of mercury. *J. Toxicol. Environ. Health* 42:1–44. [PubMed: 8169994]
- Zalups RK, and Lash LH 1997a Binding of mercury in renal brush-border and basolateral membrane-vesicles. *Biochem. Pharmacol* 53:1889–1900. [PubMed: 9256164]
- Zalups RK, and Lash LH 1997b Depletion of glutathione in the kidney and the renal disposition of administered inorganic mercury. *Drug Metab. Dispos* 25:516–523. [PubMed: 9107552]
- Zalups RK, and Minor KH 1995 Luminal and basolateral mechanisms involved in the renal tubular uptake of inorganic mercury. *J. Toxicol. Environ. Health* 46:73–100. [PubMed: 7666495]

TABLE 1.

Known and Postulated Mechanisms for the Transport of Inorganic Mercury in Various Organs

Organ	Direction of transport	Known mechanism(s)	Postulated mechanism(s)	Postulated species of Hg ²⁺
Small intestine	Absorption from lumen	None at present	Amino acid and peptide transporters, DMT1, ZIP8, MRP3 on basolateral membrane	S-conjugates of thiol-containing amino acids and peptides, mercuric ions
Kidney	Secretion into lumen	None at present	Paracellular transport, amino acid transporters, MRP (e.g., MRP2)	S-conjugates of thiol-containing amino acids and/or GSH
	Uptake at apical membrane	System b ⁰⁺	Other amino acid transporters, endocytosis	S-conjugates of Cys, Hcy, albumin and/or other amino acids
	Uptake at basolateral membrane	OAT1, OAT3	Endocytosis	S-conjugates of Cys, Hcy, NAC and/or albumin
	Secretion at apical membrane	MRP2	MRP4	S-conjugates of thiol-containing amino acids and peptides, as well as DMPS and DMSA
Liver	Uptake at sinusoidal membrane	None at present	Endocytosis, amino acid transporters, GSH transporters	S-conjugates of ferritin, albumin, thiol-containing amino acids, and/or GSH
	Export at canalicular membrane	MRP2	—	S-conjugates of thiol-containing amino acids and peptides, as well as DMPS and DMSA
Placenta	Uptake at apical (maternal) membrane	None at present	Amino acid transporters	S-conjugates of thiol-containing amino acids and peptides and/or GSH
	Export at basolateral (fetal) membrane	None at present	Amino acid transporters	S-conjugates of thiol-containing amino acids and peptides and/or GSH
	Uptake at basolateral (fetal) membrane	None at present	OAT4	S-conjugates of thiol-containing amino acids and peptides
	Export at apical (maternal) membrane	None at present	MRP2	S-conjugates of thiol-containing amino acids and peptides, as well as DMPS and DMSA

TABLE 2.
Known and Postulated Mechanisms for the Transport of Methylmercury in Various Organs and Cells

Organ	Direction of transport	Known mechanism(s)	Postulated mechanism(s)	Postulated species of CH_3Hg^+
Brain	Uptake at blood-brain barrier	System L	Other amino acid transporters	S-conjugates of thiol-containing amino acids
Erythrocytes	Uptake	None at present	OATs, D-glucose diffusive transporter, Cys facilitated transporter, Cl^- transporter	S-conjugates of GSH and/or Cys
Intestine	Absorption from lumen	None at present	OATs, amino acid and peptide transporters; MRP3 on basolateral membrane	S-conjugates of GSH, Cys, and/or CysGly
	Secretion into lumen	None at present	Amino acid transporters (e.g. System L), GSH transporters	S-conjugates of Cys and/or GSH
Kidney	Uptake at apical membrane	System B ^{0,+}	Other amino acid transporters	S-conjugates of Cys and Hcy
	Uptake at basolateral membrane	OAT1	OAT3	S-conjugates of Cys, Hcy, and NAC
	Secretion at apical membrane	MRP2	MRP4	S-conjugates of thiol-containing amino acids, peptides and/or DMPS and DMSA
Liver	Uptake at sinusoidal membrane	None at present	Amino acid transporters, GSH transporters	S-conjugates of thiol-containing amino acids, and/or GSH
	Export at canalicular membrane	MRP2	—	S-conjugates of thiol-containing amino acids, peptides and/or DMPS and DMSA
Placenta	Uptake at apical (maternal) membrane	None at present	Amino acid transporters	S-conjugates of thiol-containing amino acids
	Export at basolateral (fetal) membrane	None at present	Amino acid transporters	S-conjugates of thiol-containing amino acids
	Uptake at basolateral (fetal) membrane	None at present	OAT4	S-conjugates of thiol-containing amino acids and GSH
	Export at apical (maternal) membrane	None at present	MRP2	S-conjugates of thiol-containing amino acids, peptides, and/or DMPS and DMSA