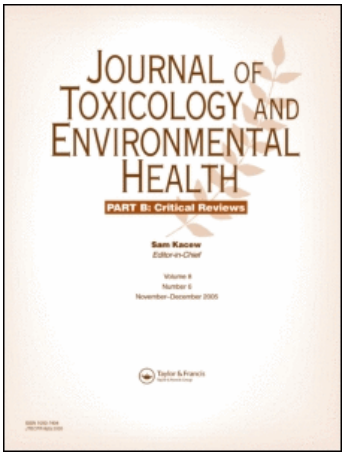


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# Transport of Inorganic Mercury and Methylmercury in Target Tissues and Organs

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# TRANSPORT OF INORGANIC MERCURY AND METHYLMERCURY IN TARGET TISSUES AND ORGANS

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**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

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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

**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 |
| | 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 |
| Kidney | 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 |



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 μmol $kg^{-1}$) 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 $b^{0,+}$. This heterodimeric transporter is comprised of two subunits, $b^{0,+}$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 $b^{0,+}$ 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 $b^{0,+}$ (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 $b^{0,+}$.

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-deficent ($TR^-$) 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 $\gamma$-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 $CH_3Hg$-*S*-Cys. These data collectively led to the hypothesis that Cys *S*-conjugates of $CH_3Hg^+$ ($CH_3Hg$-*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 $CH_3Hg$-*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



**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 |

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 $CH_3Hg$-*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 $CH_3Hg$-*S*-Cys is a transportable substrate of system L. Subsequent studies showed that Hcy *S*-conjugates of $CH_3Hg^+$ ($CH_3Hg$-*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 $CH_3Hg$-*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 $CH_3Hg$-*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 $CH_3Hg^+$ ($CH_3Hg$-*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 $CH_3Hg$-*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 $CH_3Hg$-*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 $CH_3Hg$-*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 $CH_3Hg$-*S*-G uptake at both temperatures (Wu, 1996). Subsequent studies showed that the uptake of $CH_3Hg$-*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 $y^+$, and the oligopeptide $H^+$ transport system were not involved in the uptake of $CH_3Hg$-*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 $CH_3Hg$-*S*-G. Since the luminal uptake of $CH_3Hg^+$ can be inhibited by acivicin (an alkylator of $\gamma$-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 $\gamma$-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 $CH_3Hg$-*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 $CH_3Hg$-*S*-G into enterocytes was reduced by 50%. The CysGly-*S*-conjugate of $CH_3Hg^+$ ($CH_3Hg$-*S*-CysGly), which is the first product following the action of γ-glutamyltransferase on $CH_3Hg$-*S*-G, is likely degraded further at the luminal plasma membrane of enterocytes to yield $CH_3Hg$-*S*-Cys. Any $CH_3Hg$-*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 $CH_3Hg$-*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, $CH_3Hg$-*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 $CH_3Hg$-*S*-Cys from intestinal enterocytes. Since system L was implicated in the transport of $CH_3Hg$-*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 $CH_3Hg$-*S*-G and GSH, it may be postulated that a GSH transporter, such as MRP3, may play a role in the basolateral efflux of $CH_3Hg$-*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 $CH_3Hg$-*S*-G to yield $CH_3Hg$-*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 $CH_3Hg$-*S*-G is required for the luminal absorption of $CH_3Hg^+$ by proximal tubular cells and

support the theory that $CH_3Hg$-*S*-Cys is the most readily transportable species of $CH_3Hg^+$.

$CH_3Hg$-*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 $B^{0,+}$ is capable of mediating the transport of $CH_3Hg^+$ as a conjugate of Cys or Hcy ($CH_3Hg$-*S*-Hcy; Table 2) (Bridges & Zalups, 2006). System $B^{0,+}$ 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 $B^{0,+}$ is capable of transporting $CH_3Hg$-*S*-Cys and $CH_3Hg$-*S*-Hcy in a concentration- and time-dependent manner (Bridges & Zalups, 2006). Uptake of each mercuric species was inhibited by known substrates for system $B^{0,+}$. It is interesting to note that the substrate specificity of system $B^{0,+}$ is similar to that of system $b^{0,+}$, 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 $CH_3Hg$-*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 $CH_3Hg$-*S*-G, formed within hepatocytes, is transported across the canalicular membrane into bile. Since $CH_3Hg$-*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 $CH_3Hg$-*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, $CH_3Hg$-*S*-G appears to be hydrolytically catabolized in a sequential manner by the plasma membrane enzymes $\gamma$-glutamyltransferase and cysteinylglycinase to yield $CH_3Hg$-*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 $CH_3Hg$-*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., $CH_3Hg$-*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 $CH_3Hg$-*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 $CH_3Hg$-*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.

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