

## Placental to Fetal Transfer of Mercury and Fetotoxicity

MINORU YOSHIDA

*Department of Chemistry, St. Marianna University School of Medicine,  
Kawasaki 216-8511*

YOSHIDA, M. *Placental to Fetal Transfer of Mercury and Fetotoxicity.* Tohoku J. Exp. Med., 2002, **196** (2), 79–88 — Mercury vapor is known penetrate the placental barrier more easily than inorganic mercury. A relative amount of mercury accumulates in the fetus after exposure of pregnant animals to mercury vapor. Mercury concentration in fetal organs is much lower than that in maternal organs except the liver, and fetal liver shows significantly higher mercury concentrations than maternal liver. In fetal liver, a substantial portion of mercury is bound to metallothionein (MT), which plays an important role as a reservoir of mercury during the prenatal period. The mercury retained in fetal liver is redistributed to other organs, such as the brain and kidney, with diminishing MT levels during postnatal development. Consequently, an increase in mercury concentration in the brain and kidney of the neonate is observed. In studies on animal offspring in utero exposed to mercury vapor, behavioral changes, such as radial arm maze, morris maze and lever-press durations, are observed when the levels of mercury vapor exceed the threshold limit value (TLV). ——— Mercury vapor; placental transfer of mercury; fetotoxicity; metallothionein

© 2002 Tohoku University Medical Press

Exposure to toxic metals, such as methylmercury, lead and cadmium, during gestation has potentially adverse effects on fetal development. During the outbreak of methylmercury poisoning in Japan and Iraq, it was proven that there was prenatal transfer of methylmercury through the placenta into the fetus (Harada

1968; Bakir et al. 1973; WHO 1976; Amin-Zaki et al. 1981). Later, numerous investigations on the placental transfer of various mercury compounds and the uptake of mercury by fetal tissues have been carried out (Suzuki et al. 1968; Satoh et al. 1981).

Exposure to mercury vapor is largely a

---

Received December 12, 2001; revision accepted for publication February 28, 2002.

Address for reprints: Minoru Yoshida, Ph.D., St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki 216-8511, Japan.

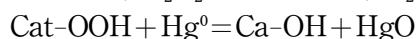
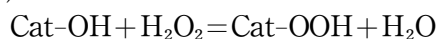
e-mail: m2yosida@marianna-u.ac.jp

This paper was presented at the Sendai Symposium: Paradigm Shift in Heavy Metal Toxicology held on November 21–22, 2001.

hazard of certain occupations, such as the production of electrolytic chlorine, electrical apparatus catalysis, paints and amalgamations, neon light workers, and thermometer workers (WHO 1991). The general population is primarily exposed to mercury through diet and dental amalgam. Particularly, mercury vapor released from amalgam fillings in the teeth of pregnant women and the increased release rate of mercury vapor by chewing are considered to be potential sources of exposure to mercury vapor of the fetus and neonates (Vimy and Lorscheider 1985; Aronsson et al. 1989; Takahashi et al. 2001). Recently, in addition to the problem of placental transfer of mercury compounds, there has been much focus on sub-clinical developmental changes in children exposed in utero or in early childhood to mercury compounds. In this paper, the placental transport of mercury vapor and its distribution in fetal organs, and the developmental effects with emphasis on neurobehavioral effects are reviewed.

#### *Metabolism of mercury vapor*

Mercury is a metal that is in the liquid state at room temperature. It has a very high vapor pressure and is rather volatile. Approximately 80% of inhaled mercury vapor is easily absorbed from the alveolar air due to its rapid diffusion through the alveolar membrane (Berlin and Nordberg 1969), most of which immediately enters the bloodstream. Uptake of mercury vapor via the skin is approximately 1% of the uptake via inhalation (Hursh et al. 1989). The dissolved vapor is then very soon oxidized to divalent inorganic mercury in red blood cells, brain, liver, lung and probably all other tissues. The oxidation is carried out via the ubiquitous  $H_2O_2$ -catalase pathway as follows (Clarkson 1997).



(Cat: catalase)

This oxidation can, however, be inhibited

by alcohol or the herbicide aminotriazole, which is an inhibitor of catalase, whereby the absorption by inhalation is considerably reduced (Halbach and Clarkson 1978; Magos et al. 1978; Eide and Syversen 1983). Although mercury vapor introduced into the body is oxidized to divalent inorganic mercury, part of the mercury vapor exists in the bloodstream for a sufficiently long time to reach the blood-brain barrier. Consequently, some mercury vapor persisting in the blood easily penetrates the barrier and accumulates in the brain (Berlin and Nordberg 1969). In contrast, the penetration of mercuric mercury into the brain is hindered by the blood-brain barrier, and brain accumulation of mercury is relatively low. Magos (1968) reported that after mercury vapor exposure, the concentration in the brain is about 10 times higher than that after administration of a corresponding dose of mercuric mercury.

#### *Mercury placental transfer and distribution of mercury in fetus*

The placenta plays an important role in the transfer of essential nutrients from the mother to the embryo and fetus. Although essential metals including zinc and copper are easily transferred to the embryo and fetus across the placenta, heavy metals such as cadmium and mercury are not transferred to the fetus. After injection of high doses of inorganic mercury to pregnant mice (Berlin and Ullberg 1963) and rats (Yang et al. 1996), significant accumulation of mercury is observed in the placenta, and a much lower accumulation in the fetus. These experiments have shown that the placental membrane constitutes a barrier against the penetration of mercuric mercury into the fetus.

On the other hand, it has been shown that mercury vapor, in contrast to mercuric mercury, penetrates the placental barrier, thereby causing the accumulation of mercury in the fetus when the mother is exposed to mercury vapor. Clarkson et al. (1972) found that mercury levels in the fetuses of pregnant rats exposed to

mercury vapor were 10–40 times higher than those in animals exposed to equivalent doses of mercuric mercury. Khayat and Decker (1982) reported that mercury vapor exposure in pregnant mice results in about 4-fold higher fetal mercury concentration than mercuric mercury injection. It has been confirmed that there is a difference in the penetration of the placental barrier among animal species. The uptake of mercury in the fetus increases with gestational age and the pattern of distribution becomes more differentiated. Only traces of radioactive mercury were found in mice embryos at 8 and 10 days of gestation, whereas a distinct accumulation of mercury was seen in fetal tissue on day 12 of gestation and later. The pronounced uptake of mercury was observed in fetal liver and heart. Yoshida et al. (1986) reported that when mother guinea pigs in late gestation were exposed to 0.2–0.3 mg/m<sup>3</sup> mercury vapor per day until birth, mercury concentrations in fetal organs except the liver were much lower than those in the corresponding organs of the mother. Mercury concentrations in fetal liver, in contrast, were about two times higher than those in maternal liver. Thus, mercury vapor metabolism in fetuses was quite different from that in their mothers (Fig. 1). Amalgam dental filling is also a source of mercury exposure. Vimy et

al. (1990) found increased mercury levels in the placenta and fetal organs of pregnant ewes having occlusal amalgam filling. The placenta progressively concentrated mercury as gestation advanced to term, and the highest concentrations of mercury from amalgam in the mother were found in the kidney and liver, whereas in the fetus the highest mercury concentrations appeared in the liver and pituitary gland. Recently, Takahashi et al. (2001) studied mercury vapor released from a single amalgam restoration in pregnant rat and measured mercury concentrations in maternal and fetal tissues. The highest mercury concentration in the fetuses was observed in the liver, and was significantly higher than those in the controls. However, mercury concentration in fetal tissues was lower than that in maternal tissues.

As described in the section “Metabolism of Mercury Vapor,” ethanol consumption modifies the balance between oxidation and reduction of mercury in the tissue. Pretreatment with ethanol reduces the oxidation of mercury vapor into mercuric mercury, and more mercury vapor exists in the blood during the exposure period. Khayat and Decker (1982) found in experiments with pregnant mice that pretreatment of dams with ethanol or aminotriazole caused a marked increase in the fetal uptake of mercury (particu-

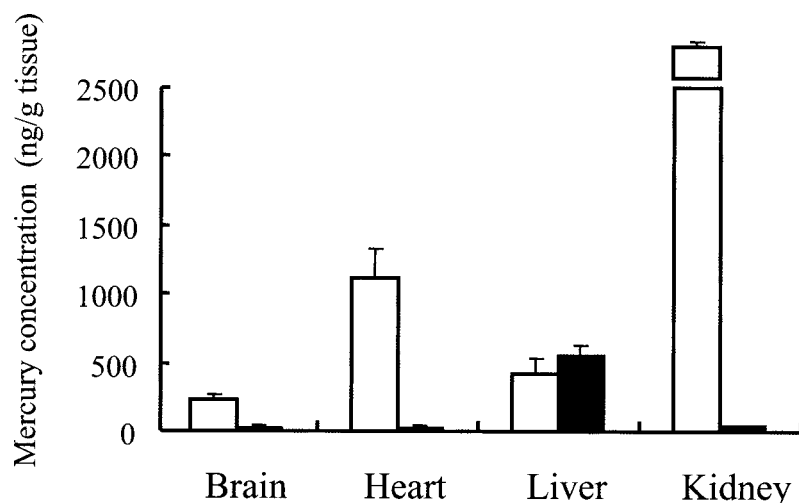


Fig. 1. Mercury distribution in maternal and fetal guinea pig after in utero exposure to mercury vapor. Modified from Yoshida et al. 1997. □; Mother, ■; Fetus.

larly in the liver) after mercury vapor exposure but not after injection of mercuric mercury. Yoshida et al. (1997) reported also that ethanol pretreatment of pregnant guinea pigs resulted in the transfer of more mercury to the fetuses and led to a marked increase of mercury in fetal liver. Ogata and Meguro (1986) found that mercury concentrations in fetuses of acatalasaemic mice, which are deficient in the enzyme catalase in the blood, were higher than those in normal mice. Thus, even if the dam is not exposed to high concentrations of mercury vapor, ethanol intentionally taken into the body may induce the increase of mercury in the fetal body.

In human, mercury vapor crosses the placental barrier, to reach the developing fetus. However, there are few data on the transfer of inhaled mercury vapor to the human fetus. In two pregnant women who had been accidentally exposed to mercury vapor, the concentration of mercury in the infant blood was similar to that in the maternal blood at the time of delivery (WHO 1991). Drasch et al. (1994) found that the mercury burden in human fetal and infant tissues increased when their mothers had a large number of dental amalgam fillings. The mercury contents in the kidney and liver of fetuses

and in the kidney and brain of older infants correlated strongly with the number of dental amalgam fillings of the mothers. Yang et al. (1997) also reported that the concentrations of mercury in the umbilical cord blood and placenta tissues of 9 parturient women who had been exposed to mercury vapor in the lamp factories were significantly higher than those of 9 non-exposed subjects. These studies indicate that mercury vapor could be transferred to the fetus via the placenta in human as well as animal experiments.

*Effect of metallothionein (MT) on mercury metabolism in fetal liver and placenta*

Metallothionein (MT) is a low-molecular-weight metal-binding protein with high cysteine content. This protein has an important role in the metabolism, transport and storage of essential metals such as zinc and copper (Cherian and Goyer 1978; Webb and Cain 1982). A high concentration of MT associated with zinc and copper is known to be present in fetal and neonatal liver (Webb and Cain 1982). Furthermore, MT concentration in the fetus is much higher than that in the mother and decreases during postnatal development. Mercury vapor passing through the placental barrier is rapidly

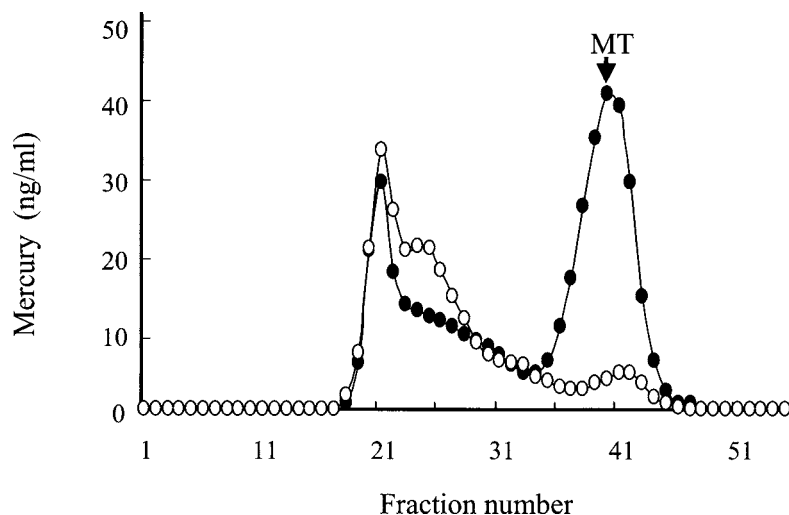


Fig. 2. Gel filtration profile of mercury in the liver cytosol from maternal and fetal guinea pig after in utero exposure to mercury vapor. Modified from Yoshida et al. 1987.

oxidized in the fetal liver and accumulates in that organ; consequently, little is distributed to other fetal organs. In the fetal liver, more than 50% of the mercury is bound to a metallothionein-like protein having a molecular weight of about 10 000–12 000 (Yoshida et al. 1987). Bulk of the eluted mercury in the maternal liver is associated with a high-molecular-weight protein (Fig. 2). These findings indicate that the fetal metallothionein-like protein plays a role in preventing the further distribution of mercury in the liver after in utero exposure to mercury vapor.

MT is also reported to be present in human and rodent placenta during pregnancy (Goyer and Cherian 1992; Lau et al. 1998). Goyer et al. (1992) described that MT is localized in the trophoblast in human placenta as well, which seems to be the primary interface between essential and non-essential metals in maternal and fetal blood. MT in rat placenta is also present mainly in trophoblastic labyrinth, spongiotrophoblast and yolk sac (Hazelhoff Roelfzema et al. 1989). A similar localization of MT was found in the placenta of mice (Yamamoto et al. 2001). The role of placental MT in maternal-to-fetal mercury transfer in MT-null and wild-type mice after exposure to mercury vapor is examined (Yamamoto et al. 2001). In pregnant mice exposed to mercury vapor at late gestation, placental mercury was localized along the boundary between the junctional zone and the labyrinth zone, as well as in the yolk sac and decidual cell and labyrinth trophoblasts. Fetal mercury levels were significantly higher in MT-null mice than in wild-type mice. Gel filtration profile of the placental cytosol in the wild-type mice revealed that a large amount of placental mercury was associated with MT and in MT-null mice appeared mainly in the high-molecular-weight protein fractions. MT in the placenta may play a role in preventing maternal-to-fetal mercury transfer.

#### *Mercury in fetal central nervous system (CNS)*

Mercury exposure during gestation results in the appearance of mercury in the central nervous system (NS) of rodents, sheep and non-human primates (Khayat and Dencker 1982; Vimy et al. 1990; Danielsson et al. 1993). The uptake of mercury in the fetal CNS differs with gestational age and is markedly less than that in the adult guinea pig brain (Yoshida et al. 1986) and in rats (Takahashi et al. 2001). Mercury concentration in the central nervous system (CNS) was rather low during early and mid gestation but increased immediately before birth (Khayat and Dencker 1982; Ogata and Meguro 1986). Pamphlett and Kum-Jew (2001) studied the localization of mercury in the CNS of the developing mice following mercury vapor exposure. No mercury was detected in the CNS of pups after fetal exposure to mercury vapor of 0.05 mg/m<sup>3</sup>. After fetal exposure to mercury vapor of 0.50 mg/m<sup>3</sup>, mercury was detected in CNS blood vessels and sensory ganglia. With a single exposure of pregnant mice to a high concentration of mercury vapor (5–6 mg/m<sup>3</sup>) at late gestation, Shimada found on autometallography that mercury in fetal brain is localized in CNS blood vessels and glial cells. Yoshida et al. (1990) reported that although mercury concentration in fetal brain after in utero mercury vapor exposure was not markedly different from that of the non-exposed group, its concentration in neonates, which were fostered by non-exposed mothers to minimize possible mercury intake through maternal milk, significantly increased during the postpartum period. They described that the significant elevation of mercury concentration in neonatal brain may be due to the redistribution of mercury caused by a progressive decrease in the amount of mercury bound to fetal hepatic MT, with diminishing hepatic MT levels in the neonates (Fig. 3). Considering the higher sensitivity of the fetus to mercury toxicity than the mother, the elevation of mercury concentration in fetal brain might

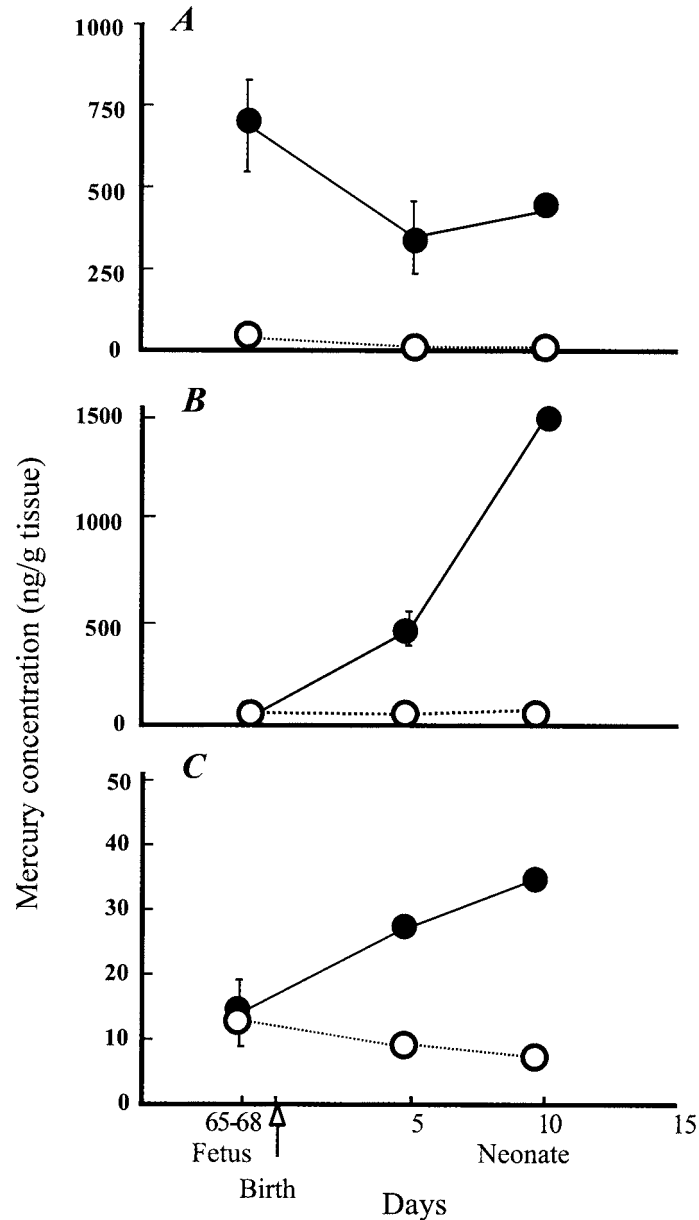


Fig. 3. Mercury concentrations in the liver, brain and kidney of fetal and neonatal guinea pigs after in utero exposure to mercury vapor. Modified from Yoshida et al. 1990.

have an adverse effect on developing neonates.

The metabolism of mercury in the fetus after in utero exposure to mercury vapor and during postnatal development is summarized in Fig. 4.

#### *Effects on fetal development*

Mercury is a well-known teratogenic agent (Koos and Longo 1976). Little is known about

the consequences of exposure to mercury vapor during development in human beings. Melkonian and Baker (1988) reported that a woman who worked in a thermometer factory had urine mercury levels of  $875 \mu\text{g}/\text{l}$  at 15 weeks of gestation, was continuously exposed to mercury throughout gestation, and delivered a viable male infant. Birth weight and neurodevelopmental status were not reported.

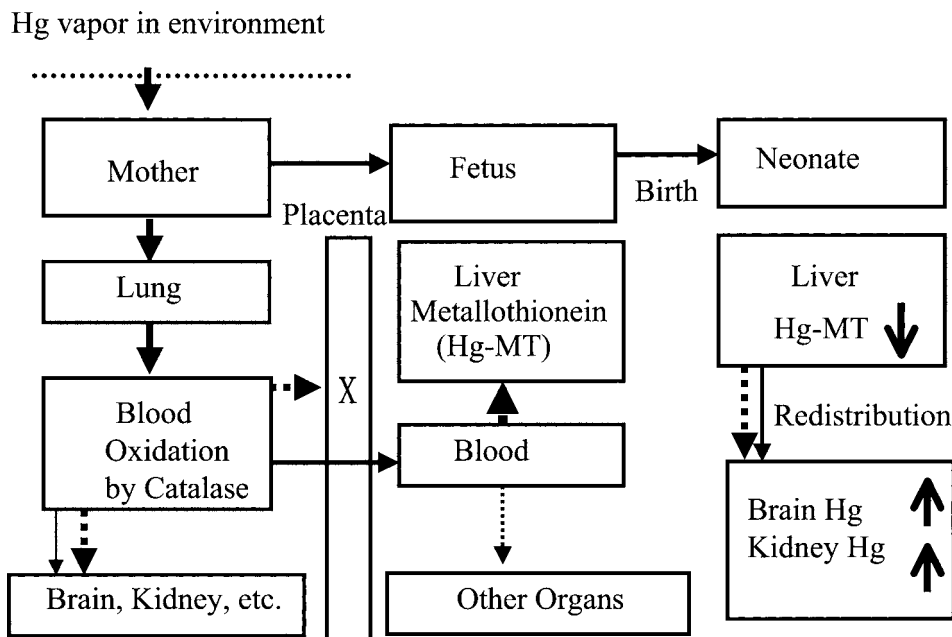


Fig. 4. Schematic representation of the transport, distribution and oxidation of inhaled mercury vapor in pregnant animals. Symbol X in the placenta represents the prevention of mercury transfer.  $\cdots\rightarrow$ ; Inorganic mercury,  $\longrightarrow$ ; Hg vapor.

Geliber and Ingram (1989) reported that 32 year-old surgeon who worked until 35th week of pregnancy in a surgery in which mercury vapor concentrations in excess of  $0.05 \text{ mg/m}^3$  had been detected, gave birth at 42 weeks to small-for-dates baby with severe brain damage. The baby's blood mercury level on the eighth day of birth was  $16 \mu\text{g/liter}$  and died the next day. In animal experiments, only a few studies have been carried out on the prenatal effects of mercury vapor. Steffek et al. (1987) reported the effects of mercury vapor on prenatal development in pregnant rats during the entire gestational period (chronic exposure) or during the period of organogenesis (acute exposure). Gross examination of fetuses from pregnant rats exposed acutely or chronically to  $0.1 \text{ mg/m}^3$  mercury revealed no increased incidence of gross congenital malformation or resorption compared to room or chamber controls. However, acute exposure at  $0.5 \text{ mg/m}^3$  resulted in an increase in the number of resorptions (5/41), and chronic exposure at this concentration resulted in two fetuses (out of 84 that were examined)

with cranial defects. A teratological study in rats indicated that embryotoxic and teratogenic effects were not observed at TLV of mercury vapor, but were observed at about 20 times TLV during the entire gestation or organogenetic period. Danielsson et al. (1993) studied the effects of inhaling mercury vapor in pregnant rats during days 11-14 plus 17-20 of gestation, approximately corresponding to doses of  $0.2$  or  $0.07 \text{ mg Hg}^0/\text{kg/day}$ , on the development and behavior of the offspring. Tests of spontaneous motor activity showed that exposed offspring were hypoactive at three months of age compared to controls, but hyperactive at 14 months. Furthermore, the prenatally exposed offspring showed retarded acquisition in the radial arm maze in spatial learning tasks and reduction of adaptability to a novel environment in a simple learning test. Christopher-Newland et al. (1996) studied the behavior of squirrel monkey offspring after in utero exposure to  $0.5$  or  $1.0 \text{ mg/m}^3$  mercury vapor during the last 2/3 or longer period of gestation. When time allocation for each lever

was examined during behavioral transitions and in the steady state, the variability in the steady-state performance was observed to be much greater in the exposed monkeys than in the control. The exposed monkeys were found to exhibit slower transitions than the control, and to have longer lever-press duration and much longer session-to-session variability at the end of the experiment. They demonstrated that long-term prenatal mercury vapor exposure led to instability in lever-press durations and steady-state performance under concurrent schedules of reinforcement as well as aberrant transitions.

Although numerous investigators have reported the effects of occupational or accidental exposure to mercury vapor on humans, the effect of low levels of mercury exposure, such as amalgam filling and fish in the diet, on the general population is as yet unknown. Larsson (1992) described that the dose of mercury vapor from dental amalgam fillings, which is of the order of 5  $\mu\text{g}/\text{day}$ , is very low compared with the TLV of mercury vapor. The embryo and fetus are known to be more susceptible to mercury compounds than adults. It is unclear whether low levels of mercury vapor can adversely affect fetal development in the absence of well-known signs of mercury intoxication. Subclinical developmental changes in children exposed in utero to a low dose of mercury vapor remain to be elucidated.

### References

- Amin-Zaki, L., Majeed, L.M., Greenwood, M.R., Ellhassani, S.B., Clarkson, T.W. & Doheety, R. A. (1981) Methylmercury poisoning in the Iraqi suckling infant: a longitudinal study over five years. *J. Appl. Toxicol.*, **1**, 210-214.
- Aronsson, A.M., Lind, B., Nylander, M. & Nordberg, M. (1989) Dental amalgam and mercury. *Biol. Metals*, **2**, 25-30.
- Bakir, F., Damluji, S.F., Amin-Zaki, L., Murtadha, M., Khalidi, A., Al-Raw, N.Y., Tikkrity, S., Dhahir, H.I., Smith, J.C., Clarkson, T.W. & Doheety, R.A. (1973) Methylmercury poisoning in Iraq. *Science*, **181**, 230-241.
- Berlin, M. & Ullberg, S. (1963) 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.
- Berlin, M. & Nordberg, F.G. (1969) The uptake of mercury in the brains of mammals exposed to mercury vapor and to mercuric salts. *Arch. Environ. Health*, **18**, 719-729.
- Berlin, M. (1986) Mercury In: *Handbook on the Toxicology of Metals*, edited by L. Friberg, G.F. Nordberg & V.B. Voulok, 2nd ed., Elsevier Science Publishers B.V., pp. 387-445.
- Cherian, M.G. & Goyer, R.A. (1978) Metallothionein and their role in the metabolism and toxicity. *Life Sci.*, **23**, 1-10.
- Christopher-Newland, M., Warfvinge, K. & Berlin, M. (1996) Behavioral consequences of in utero exposure to mercury vapor: Alterations in lever-press durations and learning in squirrel monkeys. *Toxicol. Appl. Pharmacol.*, **139**, 374-386.
- Clarkson, T.W., Magos, L. & Greenwood, M.R. (1972) The transport of elemental mercury into fetal tissue. *Biol. Neonate*, **21**, 239-244.
- Clarkson, T.W., Nordberg, G.F. & Sanger, P.R. (1985) Reproductive and developmental toxicity of metal. *Scan. J. Work Environ. Health*, **11**, 145-154.
- Clarkson, T.W. (1997) The toxicology of metal. *Critical Reviews in Clinical Laboratory Sciences*, **34**, 369-403.
- Danielsson, B.R.G., Fredriksson, A., Dahlgren, L., Reling, O., Gardlund, A., Olsson, L., Dencker, L. & Archer, T. (1993) Behavioral effects of prenatal metallic mercury inhalation exposure in rats. *Neurotoxicol. Teratol.*, **15**, 391-396.
- Drasch, G., Schupp, I., Hofl, H., Reinke, R. & Roeder, G. (1994) Mercury burden of human fetal and infant tissue. *Eur. J. Pediatr.*, **153**, 607-610.
- Eide, I. & Syversen, L.M. (1983) Relationship between catalase activity and uptake of elemental mercury. *Acta Pharmacol. Toxicol.*, **52**, 217-223.
- Geliber, A. & Ingram, J. (1989) Possible foetotoxic effects of mercury vapor; a case report. *Public Health*, **103**, 35-40.
- Goyer, R.A. & Cherian, M.G. (1992) Role of metallothionein in human placenta and rats exposed to cadmium. In: *Cadmium in the Human Environment: Toxicity and Car-*

- cinogenicity*, G.F. Nordberg, R.F.M. Herber & L. Alessio, IARC, New York, pp. 239-247.
- Goyer, R.A., Haust, M.D. & Cherian, M.G. (1992) Cellular localization of Metallothionein in human term placenta. *Placenta*, **13**, 349-355.
- Halbach, S. & Clarkson, T.W. (1978) Enzymatic oxidation of mercury vapor by erythrocytes. *Biochim. Biophys. Acta*, **523**, 522-531.
- Harada, Y. (1968) Congenital (or fetal) Minamata disease. In: Minamata disease, edited by M. Kusuna, Kumamoto University, Japan, pp. 93-117.
- Hazelhoff Roeifzema, W., Tohyama, C., Nishimura, H., Nishimura, N. & Morselt, A.F.W. (1989) Quantitative immunohistochemistry of metallothionein in the placenta. *Histochemistry*, **90**, 365-369.
- Hursh, J.B., Clarkson, T.W., Miles, E. & Goldsmith, L.A. (1989) Percutaneous absorption of mercury vapor. *Arch. Environ. Health*, **44**, 120.
- Khayat, A. & Dencker, L. (1982) Fetal uptake and distribution of metallic mercury vapor in the mouse: Influence of ethanol and aminotriazole. *Biol. Res. Pregnancy*, **3**, 38-46.
- Koos, B.J. & Longo, L.D. (1976) Mercury toxicity in pregnant woman, fetus and new born infant. A review. *Am. J. Obstet. Gynecol.*, **126**, 390-409.
- Larsson, K.S. (1992) Teratological aspects of dental amalgam. *Adv. Dent. Res.*, **6**, 114-119.
- Magos, L. (1968) Uptake of mercury by the brain. *Br. J. Indust. Med.*, **25**, 315-318.
- Magos, L., Halbach, S. & Clarkson, T.W. (1978) Role of catalase in the oxidation of mercury vapor. *Biochem. Pharmacol.*, **27**, 1373.
- Melkonian, R. & Baker, D. (1988) Risks of industrial mercury exposure in pregnancy. *Obstet. Gynecol. Surv.*, **43**, 627-641.
- Nielsen-Kudsk, F. (1965) The influence of ethyl alcohol on the absorption of mercury vapor from the lungs in man. Absorption of mercury vapor from the respiratory tract in man. *Acta Pharmacol. Toxicol.*, **23**, 263-274.
- Norgberg, G.F. & Skerfving, S. (1972) Metabolism. In: *Mercury in the Environment*, edited by L. Friberg & J. Vostal, CRC Press, Cleveland, OH, pp.29-44.
- Ogata, M. & Meguro, T. (1986) Foetal distribution of inhaled mercury vapor in normal and acatalasaemic mice. *Physiol. Chem. Phys. Med. NMR*, **18**, 165-170.
- Pamphlett, R. & Kum-Jew, A. (2001) Mercury vapor uptake into the nervous system of developing mice. *Neurotoxicol. Teratol.*, **23**, 191-196.
- Sandborgh-Englund, G., Ask, K., Belfrage, E. & Ekstrand, J. (2001) Mercury exposure in utero and during infancy. *J. Toxicol. Environ. Health*, **63**, 317-320.
- Satoh, H., Suzuki, T., Nobunaga, T., Naganuma, A. & Imura, N. (1981) Effect of sodium selenite on distribution and placental transfer of mercuric mercury in mice of late gestational period. *J. Pharm. Dyn.*, **4**, 191-196 (1981).
- Shimada, A: unpublished data
- Steffek, A.J., Clayton, R., Siew, C. & Verrusio, A.C. (1987) Effects of elemental mercury vapor exposure on pregnant Sprague-Dawley rats. *J. Dent. Res.*, **66**, 239.
- Suzuki, T., Miyama, T. & Katsunuma, H. (1968) Placenta transfer of mercury chloride, phenyl mercury acetate and methyl mercury acetate in mice. *Ind. Health*, **5**, 149-155.
- Takahashi, Y., Tsuruta, S., Hasegawa, J., Kameyama, Y. & Yoshida, M., (2001) Release of mercury from dental amalgam fillings in pregnant rats and distribution of mercury in maternal and fetal tissues. *Toxicology*, **163**, 115-126.
- Vimy, M.J. & Lorscheider, F.L. (1985) Serial measurements of intra-oral air mercury: estimation of daily dose from dental amalgam. *J. Dent. Res.*, **64**, 1072-1075.
- Vimy, M.J., Takahashi, Y. & Lorscheider, F.L. (1990) Maternal-fetal distribution of mercury (<sup>203</sup>Hg) released from dental amalgam fillings. *Am. J. Physiol.*, **258** (*Regulatory Integrative Comp. Physiol.*, **27**), R939-R945.
- Webb, M. & Cain, K. (1982) Function of metallothionein. *Biochem. Pharmacol.*, **31**, 137-142.
- WHO (1976) Environmental Health Criteria 1. Mercury, Geneva, World Health Organization
- WHO (1991) Environmental Health Criteria 1. Inorganic mercury, Geneva, World Health Organization, pp. 29-33.
- Yamamoto, E., Shimada, A., Morita, A., Yasutake, A., Yoshida, M., Nishimura, N., Suzuki, J.S., Satoh, M. & Tohyama, C. (2001) Localization and role of placental metallothioneins as a barrier against maternal to fetal transfer of mercury. *Toxicologist*, Suppl., **60**, 357.
- Yang, J. M., Jiang, X. Z., Chen, Q. Y., Li, P. J., Zhou, Y. F. & Wang, Y. L. (1996) The distribution of HgCl<sub>2</sub> in rat body and its effects on fetus.

- Biomed. Environ. Sci.*, **9**, 437-442.
- Yang, J., Jiang, Z., Eang, Y., Qureshi, I.A. & Wu, X.D. (1997) Maternal-fetal transfer of metallic mercury via the placenta and milk. *Ann. Clin. Lab. Sci.*, **27**, 135-141.
- Yoshida, M., Yamamura, Y. & Satoh, H. (1986) Distribution of mercury in guinea pig offspring after in utero exposure to mercury vapor during late gestation. *Arch. Toxicol.*, **58**, 225-228.
- Yoshida, M., Aoyama, H., Satoh, H. & Yamamura, Y. (1987) Binding of mercury to metallothionein-like protein in fetal liver of the guinea pig following in utero exposure to mercury vapor. *Toxicol. Lett.*, **34**, 1-6.
- Yoshida, M., Satoh, H., Kojima, S. & Yamamura, Y. (1990) Retention and distribution of mercury in organs of neonatal guinea pigs after in utero exposure to mercury vapor. *J. Trace. Elements. Exp. Med.*, **3**, 219-226.
- Yoshida, M., Satoh, H. & Sumi, Y. (1997) Effect of ethanol pretreatment on mercury distribution in organs of fetal guinea pig following in utero exposure to mercury vapor. *Toxicol.*, **119**, 193-201.
-