

When Does Exposure Become Poisoning: The Case of Methyl Mercury

Gary Myers, MD

Professor of Neurology, Pediatrics, and Environmental Medicine

The popular media and the medical literature¹ are full of statements that our children are being “poisoned” by environmental contaminants. Could this be true or is it simply one interpretation of available data? The term poisoning carries emotional power and suggests serious consequences. However Paracelsus, the father of toxicology, in 1538 wrote “All substances are poisons, there is none which is not a poison. It is the dose that distinguishes a poison from a remedy.” If that is true, how should we define a poison and when should the term be used?

Webster’s International Dictionary² offers the following definition for poisoning: a: to injure or kill with poison b: to treat, taint, or impregnate with or as if with poison. Wikipedia gives the following definition to poison³: “In the context of biology, poisons are substances that can cause disturbances to organisms,¹ usually by chemical reaction or other activity on the molecular scale, when a sufficient quantity is absorbed by an organism. Legally and in hazardous chemical labelling, poisons are especially toxic substances; less toxic substances are labelled “harmful”, “irritant”, or not labelled at all.” The term “poison” or “poisoning” is not very specific and appears to be used by different writers in varying ways. Many of us were trained to think that “poisoning” is associated with some clinical symptoms. However, this is not the way the term is always used.

For example, in Rochester the Coalition to Prevent Lead Poisoning reports “Last year, over 300 children were poisoned by lead in Monroe County”⁴. They base the statement on the number of children in Monroe County who had a measured blood lead level that exceeded 10 μ /dL. There have been no clinical cases of lead poisoning reported in Rochester for several years.

Such assertions are usually based on reports of toxicity from epidemiological studies. These studies evaluate sizeable cohorts of children and there are usually no individuals with clinical findings. They measure the exposure, test the children, and then statistically examine the data to determine if there are adverse associations related to the level of exposure. In the case of lead exposure, the assertion is based on reports of an adverse association of exposure with test outcomes at levels below 10 ppm^{5,6}.

These epidemiological studies are increasing in number and consequently there are a growing number of reports proclaiming environmental “poisoning”. Such assertions catch the public’s attention, generate concern, and may be important in building the political momentum to remedy the problems of pollution. However, they also generate public fear and the interpretation of the data is often complex. By design, these studies attempt to detect the most subtle difference that can be demonstrated between subjects with varying degrees of exposure. Consequently, they are complex to carry out, easily influenced by inadvertent bias, require control for factors already known to influence development, require complex analyses, and often result in findings that are open to varying interpretations. Even when the results can be confirmed, the impact of the reported statistical association may be of negligible or minimal significance.

Some of the “contaminants” that cause “poisoning”, such as heavy metals, occur naturally in our environment and we are all exposed to them. However, our exposure is often increased by pollution and other anthropogenic measures. These exposures present the population at large and Poison Control Centers with a dilemma: Are the exposures significant enough to constitute “poisoning” and do they deserve our resources and attention? Exposure to methyl mercury (MeHg) from consum-

Program Announcements ••

Ruth A. Lawrence: Monthly conference: every 4 weeks on Thursdays (11 am to noon), and every 4 weeks on Tuesdays (10 am-11 am).

UNY: The 2009 Toxicology Teaching Day is Scheduled for 11/4/09. Please mark your calendars!!

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

Long Island Regional Poison and Drug Information Center: Please look for our spring programs

Please call administrative telephone numbers for more information.

Continued on page 2

ing fish is an example of the larger issue of what constitutes poisoning.

In the 1950s at Minamata Japan a strange illness began⁷. Many causes including infectious etiologies and pollutants were suspected and eventually it was diagnosed as MeHg poisoning. The pollution came from a chemical factory that in 1935 started dumping all of its waste into the local bay. The waste included mercury, manganese, thallium, lead, selenium, iron, and other chemicals. Many of the local people consumed fish and seafood from the bay every day. Fish in the bay had MeHg levels up to 100 times more than seafood sold in the US (50 ppm as opposed to 0.5 ppm). At Minamata some pregnant mothers who were exposed to the contaminated fish and had minimal or no symptoms, but gave birth to children with severe handicaps including cerebral palsy, mental retardation, seizures, and microcephaly. The fetal exposure to MeHg and other pollutants had seriously affected their brain development. There is almost no data on the level of exposure that caused these problems, but pathological studies suggest it was very high. Outside of Japan there have been no confirmed reports of MeHg poisoning from fish consumption. Subsequently, in the 1970s, studies of fetal exposure following an epidemic of MeHg poisoning in Iraq from contaminated seed grain suggested that levels as low as 10 ppm might affect the fetus (Figure 1).

It was known that all fish contain some mercury (Hg) in the form of MeHg and consequently everyone who eats fish is exposed. In addition, with regular fish consumption exposures of 10 ppm and higher can be readily achieved. Since the United Nations estimates that nearly 1 billion people around the world consume fish daily, this was an important issue to investigate.

Finding a population with adequate exposure that could be carefully studied proved to be challenging. Several epidemiological studies were undertaken, but conditions adequate for detecting subtle changes were not always met. Our research team identified a population in the Republic of Seychelles that appeared ideal. Nearly everyone on the island consumes fish daily, but their exposure varies depending upon the amount and species consumed. The Seychelles is a small island nation with a stable, cooperative population and little emigration. The government is socialistic and provides free comprehensive basic health care and education to everyone, so some of the covariates that complicate epidemiologic studies were minimized. We have carried out an observational epidemiologic study of mercury exposure from fish consumption there over the past 25 years. The Seychellois appear to be very healthy and their athletes regularly excel in the Indian Ocean athletic contests. However, we were looking for very subtle differences between subjects with different exposures.

Since clinical experience and experimental studies indicate the developing brain is especially sensitive to the toxic effects of MeHg, we focused on prenatal exposure⁸. We took maternal hair during the prenatal visits and enrolled a cohort of nearly 800 children in 1989. To avoid inadvertent bias in analyses, we designed the study so that subjects and investigators would be blinded to exposures. We additionally specified that all primary analyses would be designed by the research team and

carried out only by biostatisticians in Rochester. We first tested the children when they were 6 months of age and then tested them regularly at intervals. We measured exposure in the mother's hair growing during pregnancy, a biomarker known to correlate with brain levels of exposure⁹. Testing started with global measures of children's cognition and development and as they matured progressed to specialized measures of specific cognitive functions. As the children reached their teens we administered the CANTAB and measured auditory evoked potentials and cardiac measures of autonomic function. This testing is still being analyzed. We have included nearly every test reported by other investigators to be associated with MeHg exposure.

We have found a number of associations between the children's exposure and their development. However, in 20 years of study no clear pattern of adverse associations has surfaced¹⁰. Indeed, we have found that some test results improve as the children's exposure increases below 10 ppm. This unexpected finding was initially puzzling since MeHg is toxic and Hg has no known function in the human body. However, Hg exposure from fish consumption may differ from other types of exposure in two ways. First, the level of exposure is lower, and second fish contain a host of nutrients that are important for development of the nervous system.

This unusual finding led us to study nutrients and their relation to MeHg exposure in a new cohort. We enrolled 300 mothers in 2001 early in pregnancy and measured iodine, iron, fish consumption, and long chain polyunsaturated fatty acids (LCPUFA). Subsequently, we tested the children on two occasions using the Bayley Scales of Infant Development (BSID). These studies found an adverse association of MeHg with the Psychomotor Developmental Index (PDI) of the BSID. However, it only appeared when the analyses included LCPUFA¹¹. Subsequent analyses examining individual and grouped LCPUFA values showed a beneficial association of the PDI with levels of omega 3 fatty acids¹². The brain is 50% lipid and LCPUFA are important components, so this finding is not too surprising. The human body cannot synthesize adequate LCP-UFA and depends on external sources such as breast milk and seafood to provide these, especially during brain development. Together, these analyses indicate that the benefits of LCPUFA from fish consumption may equal or exceed the detrimental effect of MeHg at the levels of exposure we studied.

Other authors have reported adverse associations with MeHg at exposures lower than those present in the Seychelles¹³. The subjects in that study were exposed to MeHg from consumption of whale meat which also contains polychlorinated biphenyls (PCBs), another toxin. They reported several statistically significant adverse associations of relatively small magnitude. Recently other authors have reported that children whose mothers consume more fish during pregnancy do better on cognitive testing at later ages^{14,15}. Unfortunately, their data did not include the measurement of specific nutrients like LCPUFA.

Taken together, our studies and those of others do not provide strong support for an adverse association of MeHg exposure with children's development at the levels achieved by

Continued on page 3



Question: A lactation consultant called the National Lactation Study Center drug information line. She has heard that despite the fact that the American Academy of Pediatrics listed codeine as compatible with nursing, it was no longer considered safe to use acetaminophen with codeine for pain after caesarean sections and to allow mothers to breastfeed. Is this true?

Answer:

The percentage of infants that are being breastfed when they leave the hospital has risen from 60% in 1993 to 77% in 2006 and has finally reached the 2010 target of the US Department of Health and Human Services' Healthy People goal^{1,2}. An estimated one third of all infant deliveries nationwide are now done by Caesarean Section. The question of pain management in the post delivery period in a lactating mother has become more common.

Beginning in 1983, The Committee on Drugs of the American Academy of Pediatrics published their statement on "Transfer of Drugs and Other Chemicals into Human Milk" with the last revision in 2001.³ The National Library of Medicine has developed a fairly comprehensive lacta-

tion data base.⁴ Upon review of these resources and Brigg's textbook⁵, there are relatively few reports of adverse reactions in the infants of mothers who are breastfeeding and taking codeine, although sedation has been reported. Of the 100 or so events reported from 1969 through 2002 only half were "probably" codeine related and half were "possibly" related. No event was categorized as "definitely" related. CNS depression was reported in only half the events.⁶ Over one third of the events occurred in infants less than 2 weeks of age and over three quarters occurred in infants less than 2 months of age.⁶ Only 4 cases of CNS depression were reported in infants over 6 months old and therefore, young infants were thought to be most susceptible.

In January of 2007 Madadi et al.⁷ published a case report of an infant death in a breastfed infant whose mother was taking codeine. The infant had become progressively more somnolent and developed difficulty breastfeeding at 7 days of age. On day 13 the infant was found by an ambulance crew to be cyanotic and without vital signs. Resuscitation on site and in the Emergency Department was unsuccessful. In response to this report, the FDA in August

Continued on page 4

The Case of Methyl Mercury

Continued from page 2

consuming fish. The data do provide support for the importance of nutrients present in fish for optimum development of children's cognitive abilities.

Methyl mercury is an example of a neurological toxin present in our environment to which everyone who consumes fish is exposed. Fish are a major source of preformed LCPUFA and other nutrients that are important for brain development. The benefits of nutrients from fish appear to counterbalance or perhaps exceed the theoretical risk of MeHg exposure. Exposure to MeHg at the levels achieved by fish consumption does not cause clinical poisoning. However, it is still unclear if there are subtle differences of exposure that can be detected epidemiologically at the levels of exposure resulting from fish consumption. So where should we place the emphasis? Perhaps we should return to the Hippocratic Oath which states "I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone."

REFERENCES:

1. Grandjean P, Landrigan PJ. **Developmental neurotoxicity of industrial chemicals.** *Lancet* 2006; 368: 2167-2178
2. <http://www.merriam-webster.com/dictionary/poisoning%20> accessed 2/27/09
3. <http://en.wikipedia.org/wiki/Poison> accessed 2/27/09
4. <http://www.leadsafeby2010.org/> accessed 2/27/09
5. Canfield RL, et al. **Intellectual impairment in children with blood lead concentrations below 10 ug per deciliter.** *NEJM* 2003; 348; 1517-1526
6. Surkan PJ, et al. **Neuropsychological function in children with blood lead levels <10 ug/dL.** *NeuroToxicology* 2007; 28: 1170-1177

7. Harada Y. **Congenital (or fetal) Minamata disease.** *Study Group of Minamata Disease.* 93-117. *Study Group of Minamata dDisease.* Kumamoto University, Kumamoto, Japan, 1968
8. Davidson PW, et al. **Mercury exposure and child development outcomes.** *Pediatrics* 2004; 113; 1023-1029
9. Cernichiari E, et al. **Monitoring methylmercury during pregnancy: maternal hair predicts fetal brain exposure.** *NeuroToxicology* 1995; 16(4): 705-710
10. Myers GJ, et al. **Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study.** *Lancet* 2003; 361; 1686-1692
11. Davidson PW, et al. **Nutrients from Eating Fish in Pregnancy Balance Fetal Methylmercury Exposure.** *Neurotoxicology* 2008; 29: 767-775
12. Strain JJ, et al. **Associations of maternal long chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development and Nutrition Study.** *NeuroToxicology* 2008; 29: 776-78211.
13. Grandjean P, et al. **Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury.** *Neurotox Teratology* 1997; 19: 417-428
14. Hibbeln JR, et al. **Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study.** *Lancet* 2007; 369: 578-585
15. Oaken E, et al. **Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: a study from the Danish National Birth Cohort.** *Am J Clin Nutr* 2008; 88: 789-796

Figure 1. From Cox, C, et al. **Dose-response analysis of infants prenatally exposed to methyl mercury: An application of a single compartment model to single-strand hair analysis.** *Environmental Research* 1989; 49; 318-332

2007 sent out alerts to both healthcare professionals and the public of reports of rare but significant CNS depression in infants whose mothers were taking codeine. These effects included apnea, bradycardia, and the death of this 13-day-old breastfed baby.^{8,9}

Madadi et al¹⁰ subsequently reported a case-control study of neonatal and maternal toxicity from codeine. Of 72 breastfed infants whose mothers were taking codeine, only 17 infants had signs of CNS depression. These 17 symptomatic infants had mothers whose codeine doses were almost 50% higher than the codeine doses of mothers whose infants were asymptomatic ($p < 0.05$). Mothers of symptomatic infants received 1.62(SD 0.79) mg/kg/day of codeine while mothers of asymptomatic infants received 1.02(SD 0.54) mg/kg/day of codeine. The study found concordance between maternal and infant symptoms of CNS depression. Of the asymptomatic infants, only 5/55 (9%) of the mothers had any CNS depression but of the depressed infants, 12/17 (71%) of the mothers were also exhibiting signs of CNS depression. The clinical effects noted in this study are consistent with the pharmacogenetics of codeine metabolism in humans.

Codeine is a prodrug that is metabolized into morphine by the P450 enzyme 2D6 (CYP2D6). Normally about 10% of the drug is metabolized to morphine. Morphine is eliminated via glucuronide conjugation into either morphine-3-glucuronide (inactive) or morphine-6-glucuronide (M6G) (thought to be at least equipotent to morphine¹⁰). The transformation of morphine into the active M6G is catalyzed by another enzyme uridyl glucuronosyltransferase 2B7 (UGT2B7). Any genetic variation in CYP2D6 or UGT2B7 could result in the build up of morphine or its active metabolite with resultant CNS depression or the inability to produce concentrations of morphine or M6G adequate to produce analgesia. Patients can be categorized into one of four phenotypes based on their genotype. A patient with 2 nonfunctioning alleles is a poor metabolizer of codeine and would likely produce low amounts of morphine when codeine is administered. A patient with at least one allele with a reduced function is an intermediate metabolizer. A patient with at least 1 functional allele is an extensive metabolizer and a patient with multiple copies of a functional allele is an ultra-rapid metabolizer. Ultra-rapid metabolizers produce higher than average concentrations of morphine when given codeine.

The frequency of ultra-rapid metabolizer genotypes in various ethnic groups ranges from 1% in Scandinavian populations to 10% in Mediterranean peoples to 29% in groups of Ethiopian decent.¹¹ Cases of adults who are ultra rapid metabolizers of codeine secondary to a duplication of CYP2D6 genes and have developed opioid toxicity with even small doses of codeine have been published.^{12, 13} Another study which looked at M6G production from morphine reported that adults who were homogenous for the UGT2B7*2 allele had higher M6G/morphine ratios than those who were homozygous for the wild-type allele.¹⁴

The effects of polymorphism in these two enzyme systems may be less pronounced in neonates since in full term neonates, CYP2D6 activity appears to be concordant with genotype at about 2 weeks of age but UGT2B7 activity does not reach adult levels until 2-6 months¹⁰. Therefore you would expect that mother's phenotypical variation would be more important than the infant's in the situation of a breastfeeding infant exposed to codeine. Two of the seventeen mothers of symptomatic infants in the Madadi study¹⁰ were CYP2D6 ultra-rapid metabolizers in combination with having the UGT2B7*2/*2 genotype as compared with none of the mothers among the asymptomatic neonates. Each of these mothers actually consumed 2.1-2.2mg/kg/day of codeine which is equivalent to approximately five Tylenol #3 tablets per day in a 70kg person. One of the infants died and one infant became severely toxic but recovered. Symptoms in these infants were not immediately apparent but became so after 7 days of breastfeeding. One mother of an asymptomatic infant had a CYP2D6 ultra rapid metabolizer in combination with UGT2B7*2*1 genotype and took 60mg of codeine a day for a week. The baby at this time, however, was 6 months old and was also receiving formula and solid foods.

While maternal polymorphism in CYP2D6 and UGT2B7 are important determinants in the safety of infants who are breastfeeding while mothers are taking codeine, they are not the only determinants. Doses of codeine over 0.6mg/kg, approximately three Tylenol #3 tablets per day in a 70kg mother, were also associated with infant symptoms. The most severe symptoms were associated with doses over 2mg/kg/day or approximately five tablets of Tylenol #3 per day. Older infants and infants who were not exclusively receiving breast milk were not as likely to be affected. Mothers who reported sedation themselves were more likely to have infants that were also sedated.

If codeine is to be used in mothers who are exclusively breastfeeding, the mothers need to be counseled about using the codeine sparingly and alternating doses with other forms of analgesia such as non steroidal or acetaminophen. Mothers need to be prepared to watch for infant sedation and poor feeding, especially if they themselves become sedated.

References

1. McDowell MA, Wang CY, Stephenson J. **Breastfeeding in the United States; Findings from the National Health and Nutrition Examination Surveys 1999-2006.** NCHS data briefs, no. 5 (National Center for Health Statistics, Hyattsville, MD, 2008).
2. US Department of Health and Human Services. **Healthy People 2010** (US Department of Health and Human Services, Washington, DC, 2000) http://www.healthypeople.gov/Document/html/uih/uih_2.htm#obj
3. American Academy of Pediatrics Committee on Drugs. **Transfer of Drugs and Other Chemicals into Human Milk.** *Pediatrics* 108,776-789 (2001) or <http://aappolicy.aappublications.org/cgi/content/full/pediatrics;108/3/776>

Adipose Tissue: From Depot Storage to Toxicant Target

Rick Stallhut, MD MPH

University of Rochester Environmental medicine research fellow

In the clinical research literature of recent years, it's become cliché to note that since the discovery of the fat-produced hormone leptin in 1994, we have gradually discovered that fat is not a mere energy storage depot, but instead, a complex endocrine gland deeply imbedded into the body's energy regulation system.

In toxicology, adipose tissue has been considered for decades to be a depot of another kind -- a convenient and relatively harmless place to store lipophilic toxicants like PCBs and pesticides. The basic story was this: Fat is inert -- therefore toxicants accumulating in fat is no particular threat, and may even be a beneficial sequestering mechanism -- unless, of course, sudden weight loss liberates them back into circulation. My beautiful new copy of Casarett & Doull's Toxicology (2008) unfortunately repeats this mantra.

Meanwhile, the clinical world chants a different, but related, mantra. Traditionally, obesity (and its cousin, type II diabetes) has been seen as resulting from an imbalance of a simple equation: Fat = energy in - energy out. So far, so good, but the crucial corollary to this equation is that diet, physical activity, and good moral fiber are the key to beating these diseases. It is just, they say, elementary thermodynamics.

We should have known it couldn't be that simple. Thyroid disease, for example, clearly affects weight by disturbing metabolic rate and other energy physiology. True -- physical activity would increase energy expenditure and likely help a severely hypothyroid patient -- except for the inconvenient fact that it requires immense willpower in that state to merely stay awake.

The 50,000 year view suggests even more clearly that energy regulation must be complex. Imagine you were designing a mammal for survival in a temperate climate. What are the most basic requirements of the energy system?

First, the system needs to know when energy is needed, and when it isn't. The mammal, of course, can't be too thin, but neither can it be too fat, for it needs to stay agile enough to escape predators and fight successfully for territory and mates. Second, metabolic rate should be adjustable -- greater when energy is plentiful (summer), but throttling back in winter. Third, special conditions such as periodic food scarcity or the onset of fall should ramp up transfer of serum carbohydrates into fat stores to provide additional buffering against starvation. The list goes on.

These functions are almost certainly controlled through a complex mix of neuro and endocrine signaling, the details of which we are only beginning to unravel. But even without the details, it's clear that there are many potential toxicant targets in this system -- some of which are found within adipose tissue.

So, if fat is no longer inert, then concentrating our most persistent and troublesome toxicants within it may have consequences. And given our experimentation with novel lipophilic substances over the last 50 years, we should be watching for evidence of the energy system's disruption, possibly on a large scale.

This we see -- in epidemic proportions. Obesity clearly has many causes, but disruption of functions like hunger, metabolic rate, and fat storage should certainly be on the list.

One epidemiological study, while in no way conclusive, offers a particularly intriguing clue. In 2006, Lee and colleagues published a large cross-sectional study demonstrating a strong association between persistent organic pollutant levels and prevalence of diabetes. These primary results were interesting enough, though not entirely unique. But a figure, buried back near the references offered a stunning, if underplayed, surprise.

Everyone knows obesity and type II diabetes are strongly linked, with obesity a major (though not mandatory) risk factor. In Lee's figure, they revealed that in these data, subjects with high pollutant levels displayed the typical strong association between obesity and diabetes -- but, among the lowest quartile of exposure, there was no association whatsoever. This finding suggests the startling possibility that a substantial proportion of type II diabetes could be caused or exacerbated by environmental toxicants, with obesity either a step on the causal path, or perhaps an independent effect.

Obese people are almost universally blamed for their disease, as a product of overeating and sloth. But long ago, obese hypothyroid patients were also blamed for their obesity -- until we learned to measure thyroid functions. Now we know hypothyroidism is a disease, and when that disease is treated, these "slothful" people miraculously become active and lose weight.

The hypothesis today is that a similar phenomenon, caused by environmental toxicants, is disrupting our energy regulation system. It is a bold hypothesis to be sure, but evidence is accumulating. We now need a concerted investigative effort by researchers and clinicians -- which begins with the cliché that fat is no longer depot storage, and, it follows, the possibility that fat may be a poor place to store some of our most pernicious toxicants.

Lee, D. et al., 2006. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. Diabetes Care, 29(7), 1638-44.

Melamine

Sharon Ternullo, Pharm.D. DABAT

Since 2007 melamine contamination of food products has repeatedly made world news. Melamine has been found as a contaminant of pet foods, candy, infant formula, and specialty drinks made from milk products manufactured from ingredients imported from China. The contamination of pet food manufactured in the United States was reported in February and March of 2007. The source of contamination was melamine that had been added to wheat gluten in China and then exported and used to manufacture pet food world wide. Over 100 brands of pet food were recalled in the United States alone. The confirmed number of animal deaths in the United States was at least 16, with nearly 500 cases of kidney failure. Veterinary organizations estimated the number of pet deaths to be between 2,000 and 7,000 animals and Pet Connections data, based on the self-reporting of pet owners, placed unconfirmed deaths at approximately 4000 dogs and cats.^{1,2} In April of 2007 it was determined that “melamine scrap” had been placed in fish and livestock feed and as a result of this addition, melamine contamination was present in eggs shipped from China and pork and chicken produced in the United States but fed contaminated feed imported from China.

In 2008 several Chinese companies were implicated in a scandal involving infant formula with large amounts of melamine added. Melamine powder was purchased and added to pooled, watered-down cows milk and then sold to a Chinese infant formula company. The results were kidney stones and renal failure; especially in young children. Nearly 300,000 children became ill, thousands were hospitalized, and at least 6 infants died.^{3,4}

What is Melamine?

Melamine has a structure that is 66% nitrogen by weight. The nitrogen packed molecule makes melamine useful as a fire retardant in plastics and melamine resin useful in house wares, countertops, fabrics, glues, and flame retardants. As the plastic chars it releases gaseous nitrogen. Most fires are not hot enough to burn nitrogen and therefore melamine is an effective flame retardant and melamine plastics are almost impossible to burn. The product can be manufactured chemically (China is the world’s largest exporter of melamine) and is also a metabolite formed in the body of mammals and some plants from the pesticide, cyromazine.

Because of its rich nitrogen content, melamine was trialed as a fertilizer for crops several decades ago but the slowness of the hydrolysis reactions which made the nitrogen available to the soil precluded its general use. Its use as a non-protein nitrogen source for cattle was also found inferior to other sources of nitrogen due to poor utilizability.

Toxicity

Occupational exposure to melamine may occur through inhalation and dermal contact with this compound at workplaces where melamine is produced or processed. Chronic exposure in workers can result in eye, skin, or respiratory irritation depending on the route of exposure. Chronic expo-

sure in rodents has had equivocal results in the production of bladder tumors and seems to be carcinogenic in the presence of calculi but there is inadequate data in humans to assess its carcinogenicity. The general population may be exposed to melamine via ingestion of contaminated food. Contamination of food with melamine could occur by several mechanisms: contamination of food with the pesticide cyromazine which can be converted to melamine by the mammal or plant used as the food source, the addition of melamine to nutritional sources of the food source, the decomposition of trichloromelamine used as a sanitizing agent on food processing equipment, or through accidental or deliberate addition of melamine to the final product or one of its components.

Melamine is relatively non-toxic with an acute lethal dose similar to table salt. The LD50 based on rat data is more than 3g/kg. The acceptable standard for human consumption for melamine has been set by the World Health Organization. WHO has set the tolerable daily dose at 0.2mg/kg.⁵ However, the combination of melamine and cyanuric acid (melamine cyanurate) has been found to be more toxic than either chemical alone in rodents. In cats and humans the combination of both substances in the diet can lead to acute renal failure. When cyanuric acid and melamine reach the renal microtubules they form melamine cyanurate crystals, which block and damage the renal cells lining the tubules leading to acute renal failure. For foods other than infant formulas, the FDA originally set the tolerable daily intake of melamine at 0.63mg/kg/day but decreased it to 0.063mg daily to apply an additional 10-fold safety factor to compensate for the potential for exposure to the combination of multiple melamine-related compounds. The FDA concluded that “levels of melamine and its analogues below 2.5ppm in foods, other than infant formula, do not raise public health concerns”.⁶

Chinese Food Recalls

In 2007 a pet food recall was initiated when pet food manufacturers found that their products had been contaminated with melamine and had caused serious illness or death in animals that had eaten them. In March of 2007, the US FDA found granular melamine in pet food which was traced back to the white granular wheat gluten that had been imported from a single source in China. Crystals were also found in the kidneys and urine of affected animals. Later, vegetable protein imported from China was implicated as well. In April 2007 it was determined that “melamine scrap” had been placed into fish and livestock feed so that crude protein analysis of nitrogen content appeared adequate despite using diluted or substandard amounts of protein. As a result of this addition of melamine to animal feeds, contamination has shown up in eggs shipped from China and pork and chicken produced in the United States but fed contaminated feed imported from China.

In 2008, several Chinese companies were implicated in a scandal involving diluted substandard infant formula that

Continued on page 7

had large amounts of melamine added to make it appear that the protein content met standards. None of this infant formula was imported to the United States. The widespread scope of the melamine fortification problem has resulted in documented contamination in many varied products worldwide including Chinese-made Cadbury chocolate and several types of Lipton Milk Tea Powder exported from China to Hong Kong. In September and October of 2008 the FDA reported melamine contamination in 27 different products produced abroad and imported to the U.S. that contained powdered milk protein or non-dairy creamer. These included drink mixes, coffee drinks, candies, and snacks.^{7,8}

United States Infant Formula

No Chinese manufacturer of infant formula has fulfilled the requirements to import infant formula to the U.S. Therefore only through members of the Asian Community who have directly imported Chinese-manufactured formulas, would the public have access to any contaminated formula.⁷ The FDA has found only extremely low levels of melamine or cyanuric acid in U.S.-manufactured infant formulas. The TDI for infants which includes a safety factor of 1000 fold is 0.063mg melamine/kg/day. The FDA has been collecting and analyzing samples of domestically manufactured infant formula for the presence of melamine and melamine-related compounds. To date, FDA tests have found low levels of melamine in one infant formula sample and low levels of

cyanuric acid in another.⁹ The levels are well below 1.0 ppm and the FDA safety assessment of infant formulas asserts that melamine or one of its analogs at concentrations below 1.0 ppm in infant formulas does not raise a public health concern.⁶ These amounts are up to 10,000 times lower than the amount of melamine reported in the Chinese-made infant formulas that produced mass illness in infants.

References

1. Pet Connection. Petconnection.com/recall/index.php.
2. Wikipedia.org/wiki/2007_pet_food_recalls.
3. **MSNBC.com** news services on line. *Two Face Execution over China Poison Milk Scandal*, January 22, 2009.
4. **China Puts 6 Melamine Poisoning Suspects on Trial after 300,000 Sickened**, AP Fox News.com, December 26-2008.
5. Endresz; L. "Safe Melamine Levels Named by World Health Organization" 10 December 2008, Health News. <http://www.healthnews.com/alerts-outbreaks/safe-melamine-levels-named-world-health-organization-2252.html>
6. U.S. Food and Drug Administration, **Center for Food Safety and Applied Nutrition**, November 28, 2008 pg 1-3.
7. U.S. Food and Drug Administration, **Melamine Contamination in China**, January 5, 2009 pg 1-4.
8. U.S. Food and Drug Administration, **FDA Statement, FDA Detects Melamine Contamination in Flavored Drink**, October 6, 2008 pg 1-3.
9. U.S. Food and Drug Administration, **Domestic Infant Formula Testing Results**, 1/7/09 pg. 1-8. <http://www.fda.gov/oc/opacom/hottopics/melamine/testresults.html>

DIC: Questions

Continued from page 4

4. US National Library of Medicine. **Drugs and Lactation Database. Monograph Codeine**: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/?..temp/~n.AabWWW:1>
5. Briggs, G.G., Freeman, R.K. and Yaffe S.J. **Drugs in Pregnancy and Lactation, 8th edn.** (Wolters Kluwer, Phil, PA, 2008).
6. Berlin CM Jr. Paul IM. Vesell ES. **Safety issues of maternal drug therapy during breastfeeding.** [Comment]. *Clinical Pharmacology and Therapeutics*. 85 (1):20-22, 2009 Jan.
7. Madadi P. Koren G. Cairns J. et al **Safety of codeine during breastfeeding; fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine.** *Canadian Family Physician*. 53 (1):33-35, 2007 Jan.
8. U.S. Food and Drug Administration Center for Drug Evaluation and Research. **FDA Public Health Advisory: Use of Codeine by Some Breastfeeding Mothers May Lead to Life-Threatening Side Effects in Nursing Babies.** August 17, 2007.
9. U.S. Food and Drug Administration Center for Drug Evaluation and Research. **FDA Public Health Advisory: Information for Healthcare Professionals Use of Codeine Products in Nursing Mothers.** August 17, 2007.
10. Madadi P. Ross CJD. Hayden MR. et al. **Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: A case-control study.** *Clinical Pharmacology and Therapeutics*. 85 (1): 31-35, 2009 Jan.
11. Koren G. Cairns J. Chitayat D. et al. **Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother.** *The Lancet*. 368:704, 2006 Aug 16.
12. Kirchheiner J. et al. **Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication.** *Pharmacogenomics J*. 7:257-265, 2007.
13. Gasche Y et al. **Codeine intoxication associated with ultra-rapid CYP2D6 Metabolism.** *N. Engl. J. Med.* 351:2827-2831, 2004.
14. Sawyer M.B. et al. **A Pharmacogenetic study of uridine diphosphate-glucuronosyltransferase 2B7 in patients receiving morphine.** *Clin. Pharmacol. Ther.* 73: 566-574, 2003.
15. Drendel A. **Pharmacogenomics of analgesic agents.** *Pediatric Emergency Medicine*. 8: 262-267, 2007

Acknowledgments

Gary Myers, MD
Professor of Neurology, Pediatrics, and Environmental Medicine
University of Rochester School of Medicine and Dentistry
gary_myers@urmc.rochester.edu

Richard Stahlhut, MD, MPH
Environmental Medicine
Research Fellow
University of Rochester School of Medicine and Dentistry
richard_stahlhut@urmc.rochester.edu

Sharon Ternullo, Pharm. D, DABAT
Drug Information Coordinator,
Ruth A. Lawrence Poison and Drug Information Center
Rochester, New York
sharon_ternullo@urmc.rochester.edu

FDA Safety Summaries

Digoxin, USP 0.125 mg, Digoxin, USP 0.25 mg (Caraco brand)

Caraco Pharmaceutical Laboratories and FDA notified healthcare professionals of a consumer-level recall of Caraco brand Digoxin, USP, 0.125 mg, and Digoxin, USP, 0.25 mg, distributed prior to March 31, 2009, which are not expired and are within the expiration date of September, 2011. The tablets are being recalled because they may differ in size and therefore could have more or less of the active ingredient. *March 31, 2009*

Propafenone HCL Tablets

FDA and Watson Pharmaceuticals notified healthcare professionals and patients of a recall of Propafenone HCL 225 mg tablets, a drug product used to treat cardiac arrhythmias. The drug is being recalled because some tablets may contain slightly higher levels of the active ingredient than specified. *March 23, 2009*

Zencore Plus

Bodee LLC and FDA notified consumers and healthcare professionals of a nationwide recall of all the company's supplement product sold under the name Zencore Plus. FDA lab analysis of Zencore Plus samples found the product contains benzamidenafil, an undeclared drug product and a PDE5 inhibitor. *March 11, 2009*

Transdermal Drug Patches with Metallic Backings

FDA has evaluated the composition of available patches to determine which of them contain metal components and to assure that this information is included in their labeling. Based on current information from this evaluation, FDA is working with the manufacturers of the following patches to update the labeling to include adequate warnings to patients about the risk of burns to the skin if the patch is worn during an MRI scan. *March 5, 2009*

Metoclopramide-Containing Drugs

FDA notified healthcare professionals that manufacturers of metoclopramide, a drug used to treat gastrointestinal disorders, must add a boxed warning to their drug labels about the risk of its long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia. *February 26, 2009*

Zonisamide (marketed as Zonegran, and generics)

FDA notified healthcare professionals that updated clinical data has determined that treatment with zonisamide, indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy, can cause metabolic acidosis in some patients. *February 19, 2009*

Raptiva (efalizumab)

FDA issued a Public Health Advisory to notify healthcare professionals of three confirmed, and one possible report of progressive multifocal leukoencephalopathy (PML). *February 19, 2009*

Xigris (Drotrecogin alfa [activated]) - Early Communication about an Ongoing Safety Review

FDA is aware of a recently published study, a retrospective medical record review of 73 patients who receive Drotrecogin alfa (activated), marketed as Xigris, indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death (Gentry et al.; Crit Care Med 2009). The study reported an increased risk of serious bleeding events and of death in patients with sepsis and baseline bleeding risk factors who received this product. *February 04, 2009*

Ethex Corporation Product Recall

ETHEX Corporation and Ther-RX Corporation expanded the company's previous recall notices to include prescription prenatal vitamin and iron supplement products. These generic products may have been manufactured under conditions that did not sufficiently comply with current Good Manufacturing Practices. *February 03, 2009*

Venom HYPERDRIVE 3.0

FDA notified consumers not to take Venom HYPERDRIVE 3.0, a product sold as a dietary supplement but containing sibutramine, an undeclared drug product and a controlled substance with risks for abuse or addiction. *January 27, 2009*

Clopidogrel bisulfate (marketed as Plavix)

FDA notified healthcare professionals that the makers of Plavix have agreed to work with FDA to conduct studies to obtain additional information that will allow a better understanding and characterization of the effects of genetic factors and other drugs (especially the proton pump inhibitors (PPIs)) on the effectiveness of clopidogrel. *January 26, 2009*