Mitigating Methylmercury Exposure
Study Confirms Potential of NAC as Antidote and Biomarker

Researchers have been searching for better ways to quantify and mitigate exposures to the neurotoxic methylmercury (MeHg). Results from a new animal study confirm that N-acetylcysteine (NAC), already used to treat acetaminophen overdose, may serve as a quick-acting antidote for and biomarker of MeHg exposure [EHP 116:26–31; Aremu et al.].

MeHg is created when elemental mercury released through the burning of coal, waste incineration, and other industrial processes is metabolized by aquatic microorganisms such as anaerobic bacteria. It bioaccumulates rapidly, with concentrations in some top marine predators reaching 100,000 times that of surrounding seawater. Fish consumption is the major source of human exposure. MeHg can cause irreversible brain damage, and the developing brain is especially vulnerable to its effects.

Treatments to mitigate MeHg exposure involve chelation, the administration of compounds that bind mercury, speeding its elimination from the body and thereby minimizing its toxicity. Current chelation methods can be nonspecific, depleting not only MeHg but also minerals required for normal cell function, such as calcium.

In contrast, chelation treatment with NAC does not affect levels of essential minerals. NAC, a derivative of the amino acid t-cysteine and a precursor of the antioxidant glutathione, is itself a potent antioxidant. NAC can be delivered intravenously or orally.

Clear Reception
Elucidating the Binding Characteristics of Bisphenol A

Several studies have indicated that bisphenol A (BPA), which is widely used in polycarbonate plastic and epoxy resin manufacturing, can disrupt normal endocrine function. Given that BPA’s estrogen receptor (ER) binding and interaction are 100–1,000 times weaker than those of endogenous hormones, researchers have hypothesized that BPA interacts with nuclear receptors other than ER. A recent study directly assayed BPA’s interaction with estrogen-related receptor-γ (ERR-γ), one of a family of “orphan” nuclear receptors—those for which natural ligands are unknown—and clarified the structural requirements that enable BPA to bind this receptor [EHP 116:32–38; Okada et al.].

Earlier research by the same team demonstrated that BPA strongly binds ERR-γ. The research also showed that BPA preserves ERR-γ’s high constitutive activity. Receptors with constitutive activity trigger molecular events in the absence of a ligand; specific ligands known as inverse agonists can deactivate these receptors.

The authors emphasize the importance of this investigation by noting that ERR-γ is very strongly expressed in the mammalian brain during development and in the brain, lung, and other tissues in adults; unpublished results from this group show the highest expression in the placenta. It is possible that BPA’s binding ERR-γ could affect the receptor’s role by activating transcription at the wrong times.

In the current study, adult rats were injected with NAC (1 mmol/kg) 2 hours after being exposed to MeHg (0.1 µmol/kg). The treated animals excreted about 5% of their body burden of MeHg within 2 hours, compared with less than 0.1% excreted by untreated animals. The response was transient and dose dependent, with larger doses of NAC resulting in higher rates of MeHg excretion.

These effects were not seen in preweaned rats (age 15–19 days) treated with NAC. The researchers speculate that the transporter systems needed to move the MeHg–NAC complex through the kidney do not mature until animals reach adulthood (around 30 days of age). However, oral NAC treatment in pregnant rats (10 mg/mL in drinking water) did protect their fetuses, reducing concentrations in the placenta and the whole fetus by 70–90%. In the dams themselves, NAC also reduced MeHg concentrations by 70–90% in the brain, by about 20% in the kidney, and by 60–80% in the blood and liver.

NAC’s short half-life, about 2 hours, may allow it to serve as an accurate real-time biomarker of MeHg exposure. According to the researchers, such a quick-acting biomarker could provide critical early warning of possible acute exposures, where early treatment is critical to prevent neurological damage. In the current study, MeHg excretion in animals treated with NAC was proportionate to MeHg body burden at the time of treatment. In contrast, standard monitoring techniques, which use hair analysis, can provide only a history of exposure and cannot guide immediate treatment for acute exposures. The researchers propose that future studies test NAC in adult humans as a biomarker of exposure and a possible treatment for MeHg exposure, especially for pregnant women whose unborn children are in danger of prenatal MeHg exposure.

—Kris Freeman
Science in the Courtroom
Examining Standards for Litigation-Based Research

Over the last 20 years, the term “junk science” has gained increasing use by defendants in toxic tort litigation as a pejorative phrase to discredit health effects data that do not meet some standard for scientific validity—or, some say, that are favorable to the interests of plaintiffs. Proponents of tort reform have argued that many large jury verdicts are the unjustified products of questionable scientific data presented by plaintiff lawyers to easily swayed jurors. Courts have responded by raising the bar that scientific evidence must have met before it can be considered in jury verdicts are the unjustified products of questionable scientific standards for litigation-based research. In a mini-monograph in this issue, 5 articles examine these questions and others that arise when examining the juncture of science and litigation. 

Acknowledging that conflicts of interest are an inherent component of science-based litigation, authors Ronald L. Melnick, Kristina A. Thayer, and John R. Bucher of the NIEHS conclude that public health decisions to allow exposure to possible carcinogens should not rely on untested hypotheses that are promoted to explain away adverse outcomes. Their article focuses specifically on rodent carcinogenicity studies and examines how strict attention to design and evaluation can reduce inaccurate conclusions and provide data that are useful for evaluating human health risks.

The authors cite early animal studies on benzene as an example of poor design that failed to detect carcinogenic effects, even though epidemiologic studies demonstrated a causal association between benzene exposure and leukemia in humans. Those early studies employed too few animals, insufficient controls, too short a study duration, and inadequate levels of exposure. In addition, the authors write, “evaluations that are based on incomplete necropsy or histopathology, do not combine related tumor effects, fail to adjust for differences in animal survival, or incorrectly use historical control data would not be expected to produce reliable information on chemical carcinogenesis.”

Courts, meanwhile, have also taken steps to reduce the likelihood of “junk science” influencing juries. Two of the articles in the mini-monograph, the first by Leslie I. Boden and David Ozonoff of the Boston University School of Public Health and the other by Sheila Jasanoff of Harvard University’s Kennedy School of Government, examine the assertion that science conducted to support litigation must be held to tougher admissibility standards than other science. Appeals Court Judge Alex Kosinski made this claim in 1995 in response to the Supreme Court remand in Daubert v. Merrell-Dow Pharmaceuticals, Inc., deciding that judges were henceforth required to assume roles as gatekeepers with the responsibility of culling out unreliable expert evidence. As the authors describe, many courts following Daubert have held that research conducted specifically for the purpose of a litigation is inherently less reliable than other science. Boden and Ozonoff re-examine whether litigation-based science should be treated differently from other science offered as evidence in the courtroom. They conclude that it shouldn’t. Their contentions include an assertion that cross-examination by attorneys aided by competent experts, not just journal peer review, also serves the ends of justice. They further argue that any science is subject to a variety of biases; for example, they write, studies funded by pharmaceutical companies or investments by corporations in research agendas tend to favor their own economic interest. Finally, the authors argue that tougher standards for litigation-generated science unfairly burden plaintiffs.

In her article, Jasanoff agrees that restrictions placed on litigation-based science following Daubert are misconceived because the scientific knowledge needed to resolve legal disputes often arises only in response to litigation. Rather than assign judges the role of gatekeeper, a more sensible approach, she writes, would be for judges to assume the position of referee. In this role, judges would “focus on the process through which litigation science is generated rather than on its validity or invalidity. They would be in a position to structure agreements among the parties that would be most conducive to producing relevant and reliable knowledge.”

In a fourth article, Carol J. Henry and James W. Conrad, Jr., of the American Chemistry Council focus on the role of federal agencies rather than that of the courts. They write that the quality of agency scientific research and testing is already subject to a variety of standards and practices (e.g., the Federal Information Quality Act, and peer review and transparency in research practices), and argue that these standards and practices allow agencies to judge the quality of work regardless of the reason for which it was created. They also point out that federal agencies are required to accept and fairly consider information provided by any interested person in the course of decision making.

In the last paper, William R. Freudenburg of the University of California, Santa Barbara, takes a critical look at the nature of bias itself, concluding that scientists oftentimes are not conscious of its influence on them. Drawing from personal experience, Freudenburg describes litigation-based research he conducted for a company that never tried to censor his work and consistently praised him for being principled and credible. But he subsequently came to realize that praise for his objectivity actually encouraged him to interpret his findings in ways that would favor his corporate sponsors more than if they had tried to tell him what to say. The problem, he writes, was “the temptation to start changing my own judgments . . . in response to their repeated insistence that it was precisely my independent and scientific credibility that they valued.”

The articles in the mini-monograph share a common thread: when science is used to serve the purposes of litigation or administrative proceedings, great care is needed to ensure its proper deployment, and a courtroom judge is probably not the appropriate person to decide on the reliability and relevance of scientific evidence. Furthermore, the perception that bias is inherently bad or avoidable may itself be biased. —Richard C. Dahl