THE QUARTERLY REVIEW OF ADVANCED RISK MANAGEMENT STRATEGIES

VOL. 23 NO. 3  FALL 2009

- Turbulence, Trials, and Toxic Torts
  - Managing Through the Turbulence
    Donna Galer
  - Surviving in Turbulent Times
    Jerry Theodorou
  - Challenges of Foreign Clinical Trials
    Lee W. Farrow and Robert J. Gaffney
  - Future of Class Actions in the European Union
    John Evans, James Barratt, and Collette Rawnsley
  - Consumer Product Safety Notification Requirement
    Eric A. Rubel
  - Changing Perspectives on Chemical Product Risks
    Monica M. Welt and Elizabeth L. Anderson

- ISO on Enterprise Risk Management
- ERM Process and Technology
- Commentary
- Insurance Strategies
- Loss Control
- Insurance Law

ERM and Pandemics, Part II
Best Practices
Disability Management
When Insurers Cause Bankruptcy
Product Degradation
Do Clothes Make the Man?
Changing Perspectives on Chemical Product Risks

MONICA M. WELT AND ELIZABETH L. ANDERSON

This article explores the intersection of chemical science and toxic tort law to discuss the impact of scientific advancements in chemical detection on current toxic tort litigation. The authors provide a primer on the risk assessment mechanics employed by U.S. regulatory agencies to assign safe exposure levels to chemical substances, explain the noncorrelation between those levels and causal proof of injuries when human exposure exceeds those levels, and discuss impending changes to the U.S. Environmental Protection Agency’s (EPA’s) risk assessment approach. The final section uses the recent MTBE litigation as an example of the impact of EPA’s revised risk assessment approach.
Introduction

Before a recovery can be obtained from a defendant, a toxic tort plaintiff must demonstrate that the defendant’s actions caused, or significantly increased the plaintiffs’ risk of, injury. A formal risk assessment is often required. Such assessments require knowledge of 1) likely health effects associated with the exposure at issue; 2) dose-response relationship; 3) population at risk; 4) character of the alleged toxic substance; and 5) claimant’s exposure to potentially confounding substances and effect of such exposure. Plaintiffs’ lawyers regularly cite exceedances of governmental environmental exposure standards as “proof” of health effects, even when evidence-based studies show no causation of health effects at the low levels of most exceedances. Regardless of the lack of causation-based scientific evidence, corporations devote hundreds of millions of dollars each year to defending suits based on no more proof than “exceedance.” Therefore, understanding the scientific standards and guidelines used to create the risk assessments that underlie most environmental and human exposure regulatory standards can provide strategic advantages when facing a toxic tort suit.

While our regulatory agencies are tasked with answering the question of whether and to what degree the chemicals ubiquitous to modern life — present in our food, water, air, workplace, and consumer products — pose a threat to human health, this debate has moved from the laboratory to the courtroom. Courts regularly weigh competing scientific theories to determine whether the potential future consequences of exposure to a given chemical require court-mandated medical monitoring, even when the plaintiffs can show no present injury. Similarly, the court’s ability to scientifically assess and allocate the impact of decades of permitted industrial releases as opposed to isolated violations along grossly polluted waterways determines whether the correct remedy to an illegal environmental release is extensive remediation or a fine.

Most of these legal conclusions are necessarily based on supposition and extrapolation — scientifically founded and peer-reviewed, but based only on animal studies and risk assessment — because human studies would be unethical, and real-time measurements of environmental releases are rare. The scientific community recognizes such study limitations, and the outcome-determinative impact that seemingly minor inputs can have on study conclusions. However, judges and juries are tasked with weighing complex medical and scientific theories presented by “dueling” experts. Study limitations are often ignored in the courtroom when a confidently presented “definitive” answer regarding exposure and causation, coupled with a savvy presentation, can win a multi-million dollar case.

As toxic tort litigation stands at the intersection of tort law and science, enterprise risk assessment based solely on current case decisions or current regulations is shortsighted. While accurately predicting the future of toxic tort law and liability is impossible, CEOs and business managers possessing a greater awareness of potential liabilities arising from past chemical use, scientific developments, and changing regulatory standards can better assess potential litigation risks accruing to current corporate practices and prospective acquisitions.

As toxic tort litigation stands at the intersection of tort law and science, enterprise risk assessment based solely on current case decisions or current regulations is shortsighted.

“Bet-the-company” litigations frequently arise not from intentional bad practices, but from the clash between historically acceptable practices and changing regulatory standards (often triggered by advancements in chemical detection and exposure pathway analysis). An exposure-based regulatory standard founded on risk assessments that established levels that ensure no harm, by its very definition, lacks the critical link between causation and harm when exposures exceed such levels. A basic awareness of current and developing theories regarding changing definitions of “hazardous products” and long-term exposure effects and novel methods of measuring both are essential for a decision-maker of any corporation producing, handling, or using chemicals, or acquiring real estate where these activities occurred.
Debates over human chemical exposure impacts — and related plaintiff injury claims — are not going away. EPA has committed to reassessing the human carcinogenicity of hundreds of chemicals, with more than 70 under current review as of May 2009. EPA’s assessment of these chemicals and related regulatory levels will continue to be used as evidence in toxic tort cases even when the exposure levels are unrelated to injury causality. In the next several years, EPA chemical assessment efforts will likely increase. And this increased regulation will likely spawn many more toxic tort lawsuits. Businesses aware of the current state of toxic tort liability and recent case decisions, as well as developments in the science that drives these cases, are best equipped to make decisions about their actions today.

Risk Assessment and Predicting Whether Chemicals Cause Cancer or Other Diseases

Public health agencies share a mission to prevent and preempt disease occurrence. Consequently, these agencies have developed risk assessment guidelines to derive conservative levels for exposure to substances below which no risk to human health exists. These guideline values establish the absence of risk where an exposure is below the guideline, but when the exposure exceeds the guideline, one cannot conclude the existence of a causal relationship or, necessarily, any risk. An understanding of how these guidelines were developed and how they will be shaped in the future can be used to demonstrate that these guidelines cannot provide a basis for establishing causal relationships between exposure and disease.

Nature of the Regulatory Risk Assessment Process and the Sharp Differences Between That Process and Scientific Analysis

Beginning in 1976, EPA adopted public-health-conservative regulatory guidelines for risk assessments to inform public-health-protective measures, and other public health agencies soon followed. To address scientific uncertainties and knowledge gaps, these public health agencies combine scientific data with inferential judgments (i.e., policy-based assumptions to replace gaps in scientific knowledge) to complete risk assessments intended to protect the public health. These judgments are not intended to establish causation (i.e., to define when a significant risk exists), but rather to err conservatively on the side of public health protection when setting regulatory standards and guidance levels to ensure that no significant public health risk exists.

In 1983, the National Research Council (NRC) published Risk Assessment in the Federal Government: Managing the Process (Red Book). The committee’s focus was “mechanisms to ensure that government regulation rests on the best available scientific knowledge, and to preserve the integrity of scientific data and judgments in the unavoidable collision of the contending interests that accompany most regulatory decisions.” Stressing that “the greatest improvements in risk assessment result from the acquisition of more and better data, which decreases the need to rely on inference and informed judgment to bridge gaps in knowledge,” the NRC also recognized that “[t]o make judgments amid such uncertainty, risk assessors must rely on a series of assumptions” when setting regulatory standards to protect the public health.

The Red Book leaves no doubt that the health assessment process in the public health arena is composed of two components: the science-based component, and the inference — or policy-based — component. As such, policy-based assumptions are necessary in order to complete the assessment process and allow a regulatory decision to be made in accordance with federal statutes intended to protect public health. These assessments are far different from science-based evaluations intended to establish causality or the existence of an actual risk.

The Red Book was very influential. Since 1983, public health agencies have uniformly adopted conservative approaches for evaluating scientific data that can inform public health protective measures. As recognized in the Red Book, “When scientific uncertainty is encountered in the risk assessment process, inferential bridges are needed to allow the process to continue.” These inference judgments — which are both science-based and policy-based — are not intended to establish causation, but rather are conservatively chosen components of the risk calculation that err on the side of public health protection.

Thus, there is a sharp distinction between relying on an evidence-based scientific analysis and use of the regulatory public health agencies’ risk assessment guidelines and practices. Both approaches must confront the boundaries of scientific knowledge — what is and is not demonstrated by properly performed hu-
man studies. Often, there is a paucity of information from either human or animal studies, such that the data gaps (that which is scientifically unknown) are enormous. Regulatory risk assessments and scientific analysis treat these data gaps very differently.

For some substances, epidemiology studies have established causal relationships. The first step in the risk assessment process is a qualitative, weight-of-evidence evaluation of these studies. Where there are clear associations of disease in human subjects with exposure supported by results in animal studies, the weight-of-evidence is strongest. Likewise, observations in epidemiology studies can establish at what levels of exposure or dose an agent is known to cause disease. The greatest difficulties are the lack of human data and constraints on testing human subjects: Studies in humans often show little or no evidence of health effects, and high-dose animal studies have limited value in predicting whether the observed effects are relevant to humans at the low concentrations that might occur in the environment. However, when a scientific analysis reaches a point where there is a gap in the scientific knowledge, then the analyst must withhold judgment and admit that scientific evidence does not support a particular conclusion.

Under the regulatory risk assessment process, however, the analyst employs conservative default assumptions or inferences to substitute for the gaps in scientific knowledge. In the absence of data to provide a scientific foundation for evaluating potential impacts on populations that might be regarded as particularly sensitive, regulatory agencies rely on risk assessment approaches and reference judgment to establish health protective standards and guidance levels (i.e., to err on the side of public health safety). Substituting such conservative policy judgments for unknown areas of science is reasonable public health regulatory policy for agencies seeking to develop highly conservative guidance levels that are protective of public health.

Although often used incorrectly, the results of the process are not intended to be, and do not constitute, evidence that exposures above a regulatory guidance level create a risk of adverse health effects. However, the news media and juries often miss this critical distinction when presented with “exposure evidence” of excursions above the guidelines.

The Red Book is now considered an essential text for health risk assessment. The document outlined a four-step process for risk assessment often referred to as the “risk paradigm,” which is now widely accepted and applied by governmental authorities throughout the world.

Designed to address scientific uncertainties, the process involves four primary steps:

- **Hazard Identification** — the qualitative evaluation of the weight-of-evidence from epidemiology, animal bioassay studies, and in vivo and in vitro studies assessing the agent’s capability of causing disease;

- **Dose Response** — assembly of evidence in the observed range of dose and health effect response, usually at high dose exposures in human or animal studies, to infer risk outside the observed range, where most environmental exposures occur;

- **Exposure Assessment** — assessment of likely exposures to the agent in question; and

- **Risk Characterization** — overall characterization of the weight-of-evidence concerning the likelihood that the agent may cause disease and an estimate of the potential consequences of any assessed exposure.

To evaluate the significance of exposure to an agent, the elements of risk assessment must be addressed; however, public health agencies have adopted public health-protective guidelines to address gaps in scientific knowledge. Consequently, risk assessments that rely on these guidelines can establish the absence of risk where risks are estimated to be very low but cannot be used to establish causal relationships or the existence of high risk. When low-level exposures occur, agencies charged with public health protection make an inference judgment and extrapolate to lower exposures to estimate cancer risks. The extrapolation is based on an inference judgment and not scientific data. One example is EPA’s default position in assessing chemical carcinogenicity:

When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when [it is] scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective
Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained. However, EPA acknowledged that the response to low-level exposures is uncertain:

It should be emphasized that the linearized multistage procedure [the most common no-threshold model] leads to a plausible upper limit to the risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown, and may be as low as zero. Since the 1960s, conventional science has applied margins of safety to establish safe levels of exposure for agents with potential noncancer effects. These approaches seek to identify no-observed-adverse-effect levels (NOAELs), including effects as simple as, for example, reduced weight gain, in humans. However, if no human data are available, then laboratory animal studies are substituted. Most NOAELs are based on animal studies, so an uncertainty factor of at least 100 is the basis for the margin of safety.

Margins of safety may be reduced in special cases to a safety factor of 3 or less. On the other hand, the typical safety factor of 100 may be increased by additional safety factors of 10 where study results are judged to warrant greater precautionary measures. While some rules prevail, there is no doubt that judgments differ as to how precautionary the assessors need to be. Although more refined scientific approaches are being investigated and, in some cases, applied to data that can refine these dose-and-effect relationships, these safety factor approaches are still the most conventional way of defining and providing margins of safety for noncarcinogens.

For example, other approaches to comparing exposures in animals in terms of their relevance to humans include a simple comparison of margins of exposure (MOEs) between the applied dose in animal studies and the exposure to humans, use of a benchmark dose, or use of highly complex pharmacokinetic or pharmacodynamic models and mechanistic data. EPA has placed a cap of 3,000 on the upper end of the safety factors, with the notation that uncertainties exceeding this level make the resulting guidance levels too uncertain to be of use. These examples make it clear that public health protective standards and guidance levels derived using highly conservative risk assessment guidelines, are intended to preempt disease and protect public health. They cannot provide a basis for establishing causal relationships between exposure and disease.

New Standards for Risk Assessments

On March 25, 2009, EPA released a strategic plan to incorporate advances in molecular biology and computational sciences into toxicity testing and risk assessment practices across the agency. This ambitious plan proposes a landmark transformation in toxicity testing and risk assessment over the next 10 years. Under the plan, risk assessments will rely increasingly on knowledge of toxicity pathways; the rapidly evolving science of how genes, proteins, and small molecules interact to form molecular pathways that maintain cell function; and how exposure to environmental agents can perturb these pathways to lead to adverse effects. EPA has embraced new technologies and databases as a foundation for the advances in safety assessments described in this plan. This shift to toxicity pathway-based risk assessment is a logical progression in the evolving use of better science to inform risk assessment.

The goals of the plan are to rely increasingly on in vitro tests, particularly in human cell lines, to replace expensive and time-consuming whole-animal studies for predicting human health effects. The strategy envisions the eventual use of whole-animal tests to focus primarily on mechanisms and metabolism. These new testing approaches will allow rapid testing of untested chemicals, exploration of various types of adverse effects under differing exposure scenarios, investigation of sensitive populations, and measurement of toxicity of mixtures of compounds. For example, with increasing knowledge, it will be possible to predict where interaction with multiple toxicity pathways might be expected to lead to nonadditive outcomes. Priorities for research will focus on in vitro assays for the key targets of chemicals in the environment for which limited knowledge is available (e.g., developmental, neurotoxicity, immunotoxicity, and reproductive toxicity).

All of EPA's risk assessment guidance, beginning with the earliest guidelines in 1976, encouraged the use of better science to replace default assump-
This new strategy and reports by the National Academy of Science (NAS)/NRC on toxicity testing provide a clearer, although ambitious, path forward for progress. "The evidence that new approaches are having an impact on risk assessment now is clear."

Toxic Tort Liability Ramifications Under Changing Regulatory Standards

Corporate real estate purchases do not proceed unless environmental assessments intended to identify the presence of any historical contamination are first completed as a part of regular due diligence. Many corporations still face unexpected future environmental liabilities once the examined property is purchased, despite conducting these assessments, because of changes in clean-up standards resulting from scientific advancements and the reexamination of regulatory risk assessments. Because typical environmental due diligence does not include an examination of trends and forecasting regarding changing environmental enforcement standards, such unpleasant surprises are not uncommon.

Before purchasing real estate or a corporation with real estate assets, the standard first step in the process of environmental due diligence is to commission a Phase I environmental site assessment (ESA) to determine potential or existing environmental contamination liabilities. A Phase I ESA is limited to scrutiny of the land to determine potential soil contamination, groundwater quality, and surface water quality and does not include actual testing of soil or water. The components of an ESA include the definition of any chemical residues within structures; identification of possible asbestos-containing building materials; inventory of hazardous substances stored or used onsite; assessment of mold and mildew; and evaluation of other indoor air quality parameters. An ESA with these components is generally considered sufficient to create an "innocent purchaser" defense from any future CERCLA liability for historical contamination later discovered.

However, even when a more detailed investigation involving chemical analysis for hazardous substances or petroleum hydrocarbons, known as a Phase II ESA, is conducted, neither a Phase I nor Phase II ESA would assess potential future liabilities related to chemicals present at levels below current regulatory thresholds. Unless contemplated more broadly by the purchasing corporation, the known chemical history behind a seemingly benign purchase of an industrial property can quickly spawn a multi-million dollar liability.

Regulatory standards for environmental exposure to various chemicals are changed as standards to measure exposure, bioavailability, and physiological impact become more sophisticated. Accordingly, as regulatory agencies implement new techniques and assess new scientific studies regarding toxicity and carcinogenicity, the permissible exposure levels and maximum contaminant levels are often adjusted to reflect current knowledge. Regulatory review processes are complex proceedings with time for thorough analysis, public comment, and scholarly debate. Informed corporations, and attorneys, can readily monitor chemicals that are undergoing regulatory review so as to anticipate chemicals that may soon have revised exposure levels — and anticipate new liabilities spawned by the changes. When considering a purchase of a property with levels of contamination just below regulatory levels, a more informed risk and liability assessment that considers current information of priority chemicals can have broad benefits.

EPA's Integrated Risk Information System (IRIS) is one such source. IRIS is an electronic database consisting of a compilation of electronic reports on specific substances found in the environment and their potential to cause human health effects. IRIS was initially developed for EPA staff in response to a growing demand for consistent information on substances for use in risk assessments, decision-making, and regulatory activities. The information in IRIS is intended for those without extensive training in toxicology, but with some knowledge of health sciences.

As of April 2009, EPA had at least 70 different chemical substances in ongoing IRIS assessments, but the database contains information on more than 500 chemicals. IRIS assessments are an 11-step process in which EPA investigates hazards posed by the substances. While not subject to formal rule-making requirements, EPA makes extensive use of IRIS assessments in rule-making and the setting of exposure standards. Formally, EPA emphasizes that the presence of a chemical in the IRIS database does not predetermine the outcome of any rule-making.

Each year, EPA develops a priority list of chemicals and an annual agenda for the IRIS program and announces new assessments that will begin. EPA uses five general criteria to set these priorities:
potential public health impact;

- EPA statutory, regulatory, or program-specific implementation needs;

- availability of new scientific information or methodology that might significantly change the current IRIS information;

- interest to other governmental agencies or the public; and

- availability of other scientific assessment documents that could serve as a basis for an IRIS assessment.\(^\text{15}\)

Once a chemical is designated a priority substance, EPA begins the assessment with literature searches. As the searches are completed, the results are posted on the IRIS Web site, where EPA invites the public to review the results and submit additional information.

As each assessment takes several years to complete, and the progress is easily tracked on the IRIS Web site, this is an invaluable source of information when making risk assessments regarding future liabilities.

**Biomonitoring Studies: What Do the Measurements Mean?**

Biomonitoring, the measurement of environmental chemicals in human tissues and body fluids, can provide useful data for estimating environmental exposures to naturally occurring and synthetic chemicals. The U.S. Centers for Disease Control and Prevention (CDC) has collected biomonitoring data in conjunction with the National Health and Nutrition Survey (NHANES) to determine both population exposures to various chemical substances and national exposure trends and to judge whether public health interventions have been successful in reducing exposures to toxicants, such as lead and secondary smoke.\(^\text{16}\)

The CDC National Reports on Human Exposure to Environmental Chemicals have increased public awareness and concern that various environmental chemical substances can be found in body fluids (blood and urine) and tissues throughout the U.S. population. However, the very low levels reported by the CDC are not necessarily synonymous with adverse health consequences. CDC has emphasized in the July 2005 report that the mere detection of a chemical substance in urine or blood should not be misinterpreted to indicate a health risk or potential disease in individuals or the U.S. population:

\[\ldots\] for many environmental chemicals, we need more research to assess health risks from different blood or urine levels. The results shown in the Third Report should help prioritize and foster research on human health risks that result from

---

**Exhibit 1**

**Minimum Requirements for a Scientifically Credible Biomonitoring Study**

1. Includes a clear statement of objectives.
2. Provides an overview of the state of knowledge in relation to the study objectives.
3. Lists those factors affecting levels and groups that might have different exposure levels.
4. Plans for communication to study participants, stakeholders, and the general public on state of knowledge and what the study can and cannot determine.
5. Utilizes a sample size that has substantially similar characteristics to the target population and sufficient statistical power for detecting differences.
6. Employs and documents use of validated sampling procedures and validated analytical methods and adherence to appropriate laboratory quality assurance and quality control programs.
7. Presents all, not a selective listing, of the results.
8. Uses appropriate statistical analyses and provides a balanced interpretation of the data, indicating strengths and weaknesses of the study.
9. Subjects findings to an independent peer-review before the results are published.
exposure to environmental chemicals ... the presence of a chemical does not imply disease. The levels or concentrations of the chemical are more important determinants of the relation to disease, when established in appropriate research studies, than the detection or presence of a chemical.\(^\text{17}\)

Assessment of biomonitoring results can be used to evaluate prior exposures, but the study design, study conduct, and data analyses must adhere to rigorous scientific standards in order to evaluate potential health implications. When evaluating human biomonitoring investigations and reports, it is also important to consider the extent to which these meet scientific standards of practice.

Exhibit 1 presents a list of many, but not all, of the critical elements needed for a scientifically sound biomonitoring investigation.

The July 25, 2006, NAS/NRC Committee on Human Biomonitoring for Environmental Toxics report Human Biomonitoring for Environmental Chemicals extensively evaluates the state of the science and provides recommendations for study design, data interpretation, communications, and research needs to advance the field.\(^\text{18}\) NAS has concluded that:

The ability to generate new biomonitoring data often exceeds the ability to evaluate whether and how a chemical measured in a population may cause a health risk or to evaluate its sources and pathways for exposure.\(^\text{19}\)

NAS also cautioned that not all biomonitoring surveys should be equated to the CDC NHANES evaluations:

Because not all biomonitoring studies are conducted with the same rigor, it is important that the guidelines presented be followed to ensure, to the extent possible, that biomonitoring studies will lead to the identification of chemicals that are causing risk or health effects, will provide information on exposure pathways and health effects to guide future control efforts and will avoid anxiety or apathy about chemicals where personal or societal risks appear not to warrant that reaction.\(^\text{20}\)

The NAS Report outlines a continuum of risk assessment and management activities related to exposure biomonitoring comprised of four key elements:

- **Scoping**: screening; exploratory investigations; source investigations; and societal hazard identifications;
- **Status and Trends**: exposure surveillance; population research; pathway research; decision validation; and health surveillance;
- **Exposure**: epidemiology research; toxicological research; pharmacokinetic and pharmacodynamic research; and community and occupational investigations; and
- **Risk Assessment**: population risk characterizations; clinical applications; and individual risk characterizations.\(^\text{21}\)

**Biomonitoring Studies: Design and Limitations**

Some nongovernmental biomonitoring surveys may be so limited in design that they do not meet any of the NAS risk assessment continuum criteria\(^\text{22}\) or have been conducted on such a small scale so as to meet only the specifications for a scoping study. NAS has stated that for biomonitoring, scoping is a basic activity that “may provide the first indication of a potential problem.”\(^\text{23}\) Thus, by their very nature, most small-scale studies cannot provide scientifically meaningful, quantitative data on trends, epidemiology, or conclusions about health risks.

Small sample size and nonrandom selection of biomonitoring survey participants also precludes the possibility of making scientifically supportable, unbiased comparisons among various subpopulations. Potential confounding factors, such as age, weight, diet, health issues, workplace, and genetic factors, should be considered when assessing environmental exposures.

The detection of a chemical or its metabolites in urine or blood, however, is not a standalone means to evaluate individual or population risk. Scoping generally determines only whether a chemical is detected in the biomonitoring sample but not what that means. Conversely, the presence of other more toxic substances, either natural or synthetic, may be overlooked because they were not analyzed. Few small-scale biomonitoring surveys meet NAS standards for use in trends, epidemiology, or health risk
assessment. Moreover, interpreting the results from small biomonitoring surveys directly to population risk assessment skips over key exposure analyses of data from animal toxicology studies, epidemiology, pharmacokinetics, and genetic factors that are essential in determining the significance of exposures.

NAS also identified ethical considerations and communications, interpretations, and use as high priorities. The protocols and study designs of biomonitoring surveys, involving any number of participants, should undergo evaluation by Institutional Review Boards (IRBs) before the studies are initiated (at the design stage). Biomonitoring survey results should be independently peer-reviewed before reports are published or made public. Because human subjects are involved, it is essential that scientifically responsible and clear reports be issued that explain the results to the public. Failure to account for ethical issues of communicating biomonitoring data in the context of public health risk may raise undue concerns and fear in study volunteers and the public.

To summarize, biomonitoring is an important tool that can be applied to better understand exposures to chemicals in our environment. The recommendations in the July 2006 NAS report provide comprehensive scientific and ethical guidance to conduct and interpret biomonitoring surveys and to communicate their results. Small-scale biomonitoring surveys that do not follow the NAS guidance often cannot reach scientifically valid conclusions because they may involve too few individuals and lack scientifically robust study designs. Despite their limitations, these limited studies are frequently presented as evidence of harm.

**Biomonitoring Results: Will Biomonitoring Results Lead to More Conservative Risk Assessments With Implications for Toxic Tort Liability?**

There are indications that regulatory agencies may be more conservative in their approaches to risk assessment as a basis for setting public standards and guidance levels where biomonitoring results have found widespread accumulation at some level in humans. It is tempting to imply that public health impacts are defined by the existence of low levels of substances found in biomonitoring studies or that these public health levels are used to suggest that medical monitoring is necessary or that, in fact, causal relationships exist between biomonitored levels and disease. Further, public health standards and guidance levels are often used in toxic tort cases in an attempt to define the levels for establishing causality or the need for medical monitoring. As discussed, public health agencies’ risk-assessment-derived guidance levels cannot be used to establish causality or the need for medical monitoring. Nevertheless, these uses persist.

Biomonitoring risk assessments attempt to incorporate the levels of toxicants found in human biomonitoring studies into various approaches to adjust the estimated exposures from all sources (the external dose) to the resulting levels found in the human studies. Many uncertainties accompany these analyses, including accounting for all exposure sources and understanding the mechanisms of disease. Since the necessary pharmacokinetic data generally are not available, various compounding-conservative approaches and adjustment factors are leading to highly conservative guidance levels. These levels are unnecessarily restrictive when compared to levels calculated with standard risk assessment approaches discussed earlier, such as EPA’s adopted cut-off of 3,000 for total use of safety factors. Moreover, the conservative calculations increase exponentially when assessors attempt to equate results from high-dose biomonitoring animal studies to human exposure levels.

If EPA implements its 2009 pronouncement of using biomonitoring-focused risk assessments to revise the established standards and guidance levels for other chemicals identified in biomonitoring studies, the implications of far more conservative allowable values for many chemicals is highly likely.

As these standards and guidance levels are employed in legal battles, there are understandable challenges involved in explaining their true meaning. Routinely, these guidance levels are misused to imply that health impacts have occurred, or are likely to occur, from either the levels found in human subjects or from levels found in the environment. For example, studies based on EPA’s risk assessment methodology, rather than site-specific exposure studies, are commonly used to attribute unfounded findings of causality to these risk assessments, arguing that exposures above these levels must be evidence of harm.

For example, EPA and several state agencies have used biomonitoring-focused risk assessments as bases for establishing guidance levels for perfluorooctanoic
Risk assessments for PFOA, resulting guidance levels, uncertainty choices that include the standard uncertainty factors, and other adjustments to take into account the intended dose from biomonitoring studies produced draft guidance levels between 15,000 and 15,700,000 ppm below the levels where effects have been observed in rodent or primate studies. Far greater than the typical EPA cut-off of a maximum uncertainty limit of 3,000, the biomonitoring focus creates exposure levels unrelated to any observed health effects. PFOA and other perfluorinated chemicals are a ubiquitous — and controversial — class of chemicals used to manufacture a wide range of consumer products, including Teflon nonstick cookware, Gore-Tex waterproof fabrics and Stainmaster carpets. However, the courts have begun to lose patience with plaintiffs who argue that exposures above regulatory levels, which are based on biomonitoring-focused risk assessments, constitute causal proof of increased risk or harm.

In late 2008, rulings in three putative class actions in federal court held that PFOA risk assessments could not be used in legal arguments to show exposure to a class of plaintiffs or to show that their exposure subjects them to greater than background risk. First, in September 2008, the U.S. District Court for the Southern District of West Virginia ruled in Rhodes, et al. v. E.I. DuPont DeNemours and Co. that public health agencies’ safety levels for PFOA in water cannot be used to establish the need for medical monitoring from PFOA exposure. Specifically, the court noted, “a risk assessment is of limited utility in a toxic tort case, especially for the issue of causation, because of the risk assessment’s distinct purpose. Risk assessments have largely been developed for regulatory purposes and thus serve a protection function in providing a level below which there is no appreciable risk to the general population. They do not provide information about actual risk or causation.”

Similarly, in December 2008, the court in Rowe, et al. v. DuPont determined that plaintiffs had not provided “any proof that any class member (let alone all class members) has reached that level of significant exposure,” instead relying on risk assessments that the judge concluded did not prove exposure.

In Rowe, the plaintiffs retained an expert to conduct a risk assessment specific to the case. But the court dismissed this effort as relying on “reported averages” of potential class members’ weights and water consumption levels, because the expert used EPA methodology assuming each person weighs 70 kg., and consumes 2 liters of water daily. In ruling that the New Jersey plaintiffs had not provided sufficient information for her to determine class status on any of the nonmedical monitoring claims, Judge Bumb explained that “[r]ather than relying on assumptions about exposure, the Rowe Plaintiffs should have conducted more extensive research concerning the proposed class members’ characteristics related to their exposure,” such as surveying residents of Parkersburg or testing their blood.

While these rulings demonstrate critical judicial understanding that regulatory guidance levels derived from regulatory risk assessments cannot be used to establish the need for medical monitoring from chemical exposure, similar class actions continue to be filed.

### Changing Information About Exposure Pathways

In addition to amending acceptable exposure levels, regulatory agencies have also amended previous risk assessments to address new concerns regarding exposure pathways when a chemical begins to appear in different forms than initially anticipated. A clear illustration of a chemical exposure limit amended in response to changing exposure pathways is methyl tertiary butyl ether (MTBE). Notably, the revised exposure limits did not purport to address new scientific data regarding anticipated health effects, but reflected a shift in perspective and purpose intended to address the fact that the most common exposures were no longer inhalation, but instead ingestion through groundwater. Specifically, the agencies sought to regulate the maximum contaminant level to address taste and odor concerns arising from MTBE in groundwater.

The Appendix explores the unpredictability of the regulatory risk assessment process, including the unanticipated corporate liabilities created when previously accepted evidence-based conclusions are abandoned to address pressure from plaintiffs’ attorneys. This case is a model of the role that independent scientific study can play in clarifying key issues in toxic tort cases, and the legal impacts of shifting agency philosophy.

Although EPA designed and ordered the foundational Toxic Substance Control Act studies in 1988
for the MTBE risk assessment and approval, EPA changed course 15 years later to address changing approaches to risk assessments. With the stated goal of applying “the most up-to-date science and to incorporate new science as it becomes available in assessing the risks associated with environmental exposures to carcinogens,” EPA sought to apply its new guidelines for cancer risk assessment to MTBE. Although the historical facts show that the agency knew about MTBE’s characteristics and potential to broadly contaminate groundwater as early as 1979, previous extrapolations of inhalation data were viewed as questionable for generating accurate ingestion exposure limits 20 years later.

Although the new MTBE IRIS assessment under the revised cancer risk assessment guidelines is scheduled to conclude in late 2011, this deadline has already been pushed back by five years and could be further delayed. The interagency review of the assessment scheduled for mid-2006 has not yet occurred; it is presently scheduled for late 2009, to be followed by external peer reviews and a final assessment. Regardless of the new assessment outcome, industry defendants have already paid extraordinary damages for the proper use of a product that was approved by EPA.

Conclusion

Predicting changes in toxic tort and environmental liability is an inexact science, but industries should contemplate possible litigation trends under today’s revised chemical exposure standards. To predict and properly mitigate risk, corporate entities would be well served to pay attention to the shifting risk assessment policies and scientific advancements instead of relying solely on current regulations and case law.

Endnotes

3. Ibid.: 1.
5. Ibid.: 12.
12. Standards for performing a Phase I site assessment have been promulgated by EPA and are based in part on the American Society for Testing and Materials (ASTM) Standard E1527-05. See “EPA Standards and Practices for All Appropriate Inquiries — Final Rule” and “ASTM Test E1903.”
13. IRIS can be accessed at www.epa.gov/iris/.
14. IRIS, ibid.
17. Ibid.
19. Ibid.
21. National Research Council, id., Table 3.1, p. 54.
22. For example, see “Polluted Children, Toxic Nation: A


27. Scott v. E.I. du Pont de Nemours & Co., D.N.J., No. 06-3080. Plaintiffs in the Scott case relied on the New Jersey Department of Environmental Protection’s risk-based 0.04 ppm safety standard for PFOA in drinking water, arguing that the levels of PFOA in the Penns Grove water supply were “up to five times higher” than the standard. But Judge Bumb dismissed the argument as “having offered no evidence of the potential class members’ exposure.”

28. Ibid.

29. Rowe, id.


Monica M. Welt is a counsel with Crowell & Moring LLP. Her practice focuses on environmental tort litigation and mass tort litigation, where she has developed extensive expertise utilizing scientific experts in client cases. Her defense experience in state and federal courts includes cases involving alleged “neighborhood” exposure to contaminants in groundwater, soil and air from petroleum, chlorinated solvents, PAHs, beryllium and mixed chemicals, resulting in claims of personal injury, diminished property value, emotional distress, and entitlement to medical monitoring as a result of occupational and environmental exposure. Welt was previously a member of a national coordinating defense counsel team for two major petroleum producers in the multi-district litigation involving MTBE contamination of groundwater before Judge Shira Scheindlin. Welt received her J.D. from the University of Virginia and dual B.A. degrees from The Ohio State University.

Elizabeth L. Anderson, Ph.D., FATS, is group vice president and principal scientist for health at Exponent. She was co-author of the first federal policy at the Environmental Protection Agency to create risk assessment and risk management as a basis for regulating environmental contaminants. Subsequently, she founded and directed the Agency’s central risk assessment activities for 10 years. She is also a founder, past president, and fellow of The Society of Risk Analyses and was editor-in-chief of the peer-reviewed journal Risk Analysis: An International Journal for 10 years.
Appendix

Case Study: EPA, MTBE, and the Inhalation/Ingestion Extrapolation Paradox

In the mid-1980s, when EPA ordered the future phase-out of lead from automotive gasoline, gasoline producers began searching for a replacement octane booster. Methyl tertiary butyl ether, otherwise known as MTBE, became the replacement oxygenate focus of both the government and the industry. Before approving the increased use of MTBE in gasoline, EPA required the industry to conduct studies and risk assessments of the potential health or environmental effects of MTBE in accordance with Section 4 of the Toxic Substances Control Act (TSCA).

The MTBE TSCA Testing Consent Order specified that the proposed inhalation study would address concerns regarding human exposure to MTBE via ingestion of drinking water containing MTBE, specifically “to relate oral, dermal, and inhalation routes of exposure.” EPA’s order addressed the ingestion of MTBE: “MTBE vapor exposure via gasoline was the major concern [. . .] EPA has an additional concern about MTBE contamination of groundwater.” While the testing ordered by EPA concentrated on human exposure through inhalation, EPA was clear that “this testing battery is more than adequate to evaluate MTBE for the effects identified by the ITC” including ingestion. From 1989 to 1992, the industry sponsored two-year inhalation bioassays with laboratory rats and mice, as well as standard tests of neural, reproductive, and developmental toxicity and mutagenesis. Test data submitted to EPA over the next four years concluded that exposure to MTBE did not pose a significant hazard or substantial risk to humans. Basically, after extrapolating data from inhalation studies, EPA determined that because there were no adverse effects from inhalation, there would likewise be no adverse effects from ingestion.

In the early to mid-1990s, it was discovered that leaks from underground storage tanks at gas stations across the United States had fouled the taste and odor of countless groundwater aquifers. In 1997, EPA reiterated that clean-up levels (ranging from 20 to 40 ug/l), intended to address these taste and odor issues, also created “margins of safety . . . about 10 to 100 times greater than would be provided by an EPA reference dose (RfD) to protect from noncancer effects.” Regardless, in 1998, EPA reopened its risk assessment of MTBE, and by 2000, EPA announced additional exposure studies:

As a result of substantial scientific uncertainties, a review committee of the National Academy of Sciences (NAS) recommended that additional studies be conducted on MTBE . . . A number of ongoing studies by EPA, the Chemical Industry Institute of Toxicology (CIIT) and other organizations should provide EPA with information to assess health risks via different routes of MTBE exposure.

These “different routes” of exposure included ingestion via drinking water, as EPA was no longer comfortable with extrapolating from previous inhalation data.

The push for more inhalation studies paralleled the filing of numerous lawsuits by municipalities and state attorneys general throughout the United States for groundwater contamination caused by MTBE. Between late 2003 and early 2004, approximately 60 suits were filed on behalf of approximately 150 water providers or governmental entities against more than 75 defendants in 16 states, alleging that gasoline containing MTBE leaked from underground storage tanks and polluted groundwater. The majority of these cases were consolidated into multidistrict litigation in New York federal court (MDL 1358).

In a novel assertion of enterprise liability, these suits alleged that liability ran to the gasoline-producing companies for adding MTBE to gasoline, rather than to the individual gas stations owning the leaking storage tanks. Plaintiffs’ liability assertions centered on whether the producers fully disclosed all relevant information to EPA leading up to the approval of MTBE. Notably, those involved in the passage of the Clean Air Act amendments disagreed:
As chairman of the Senate Committee on Energy and Natural Resources when the 1990 Clean Air Act amendments were put in place, I can assure you Congress and the EPA went into the MTBE process with eyes open. We recognized that, among the fuel additives the government was mandating for use in cleaning smog-prone city air, MTBE was the only commercially viable alternative at the time. MTBE’s water solubility risks and ability to clean the air were trade-offs we faced.\(^9\)

Some plaintiffs also asserted that gasoline producers misrepresented or omitted the hazards of MTBE. They claimed that the industry failed to conduct sufficient testing to develop accurate ingestion exposure levels and that some data show a causal link between MTBE ingestion and certain cancers.

Calls for additional ingestion studies became a favorite battle cry for MDL 1358 plaintiffs.\(^10\) As stated by plaintiffs’ attorney Robin Greenwald, “We weren’t saying that 20 years from now all of America will be riddled with cancer because they drank water with MTBE. We were saying that you can’t put a chemical in a product that you know is going to get into water without doing appropriate studies to determine its health impact. It didn’t even do a chronic ingestion study on rats.”\(^11\) Under this pressure, EPA's previous risk assessment of MTBE exposure through contaminated groundwater was deemed insufficient, and the missing ingestion study became one of plaintiffs' oft-cited points against the industry defendants in MDL 1358.

But the science did not support the plaintiffs. In 1991 and 1992, EPA used data from the TSCA studies and chronic exposure studies to calculate an inhalation reference concentration of 3 mg/m\(^3\). This was magnitudes above the calculated “worst case” chronic inhalation exposure scenarios time-weighted average exposure levels of 0.2 mg/m\(^3\), at which any appreciable risk to the general population for noncancer health effects from MTBE was deemed highly unlikely.\(^12\) And risk assessments conducted by the World Health Organization, the European Commission, the International Agency for Research on Cancer, and the U.S. National Toxicology Program all concluded that the scientific data did not support classifying MTBE as a human carcinogen.

Moreover, after several chronic animal studies, only one study linked MTBE with excess lymphoma/leukemia — and the reliability of those data was suspect.\(^13\) In a reanalysis, those data were deemed more consistent with the lymphoma/leukemia increase either being a chance finding unrelated to treatment or being related to chronic respiratory disease. Regardless, because it was the only chronic ingestion study of MTBE, the plaintiffs focused on these questionable results.

When EPA announced that a draft of the reassessment would be released for interagency review in mid-2006, rumors circulated that the draft might conclude that MTBE should be considered a likely human carcinogen. Due to the lack of reliable scientific data, some were concerned that EPA’s conclusion would be based on political pressure and the precautionary principle and, as such, would not be science-based.

At the same time, several MDL 1358 defendants commissioned and sponsored a two-year, chronic and subchronic physiologically based pharmacokinetic rat ingestion study in 2006. Designed by a panel of environmental toxicology and MTBE pharmacokinetics experts, this new study incorporated lessons from other MTBE pharmacokinetic studies and followed best laboratory practices. Intended to address the questionable Belpoggi data and determine whether those findings were reproducible, the study also included a 12-month interim sacrifice in the male rats to provide insights on the mode of action for kidney tumors.

The sponsors hired Chemical Industry Institute of Toxicology, which had performed EPA’s previous MTBE studies, to conduct the study and budgeted more than $4.5 million dollars for funding and expert oversight, and imposed no limitations on the expert panel. EPA was notiﬁed of the planned study. The interagency release of the draft IRIS assessment was subsequently delayed, with the new release timeline
postdating the study's estimated conclusion. Although the two-year dosing regime recently concluded, results of the drinking water ingestion studies have not been published.

In May 2008, while the study was underway and on the eve of beginning bellwether trials, MDL 1358 settled. In the largest settlement in the history of MTBE litigation, the settling companies, including BP, Chevron, Citgo, Shell, and Sunoco (but excluding ExxonMobil), agreed to collectively pay an unprecedented $424 million. The possible impact of the results of the drinking water ingestion study on the litigation is unknown.

2. TCO: 10392.
3. Ibid.
6. Testimony of Cynthia C. Dougherty, Director, EPA Office of Ground Water and Drinking Water, Before the Committee on Environmental and Public Works, United States Senate (December 9, 1997).
10. “A pressing need exists to complete pharmacokinetic modeling and cancer mechanistic studies of MTBE, which would allow extrapolation from inhalation data to estimate oral toxicity risk. A sub-chronic study of MTBE in drinking water is also needed to evaluate oral toxicity and help validate the extrapolation from inhalation to ingestion. Filling these needs will enhance risk assessment and risk management efforts related to oxygenated fuels.” Davis, J., “An Overview of Health Issues for Fuel Oxygenates,” Environmental Protection Agency Science Inventory, available at http://cfpub.epa.gov/si/si_public_record_Report.cfm?dirEntryId=62860&CFID=32772239160146cTR20302e30.