

Letter to our Readers

May 2007

Dear Colleague,

Epidemiology is being used increasingly to determine whether environmental contamination at a site affects the health of people who live and work nearby. In this issue of *Trends*, we examine how the results of epidemiology studies may be used to inform risk assessments, whether for sites or products. We also consider the difficult topic of determining when apparent disease clusters are related to environmental contamination.

Contributors to this issue include Dr. Julie Goodman, leader of Gradient's epidemiology practice; Dr. Lorenz Rhomberg, Gradient Principal and quantitative risk assessment expert; and Mr. Todd Hudson and Ms. Ari Lewis, both Gradient toxicologists. Joining them with our guest editorial is Dr. James Collins, the Epidemiology Director at the Dow Chemical Company, who shares his thoughts on what can be learned from quantitatively analyzing multiple epidemiology studies.

We hope this issue of *Trends* will provide you with new insights as you consider the use of epidemiology data to help analyze your sites or products.

Yours truly,



Neil Shifrin, Ph.D.  
 President and Founder

# Epidemiology and Risk Analysis

By Julie Goodman, Ph.D., DABT

*Several types of epidemiology studies are available to inform a variety of human health risk questions.*

Epidemiology is the study of the distribution of, and contributors to, disease in human populations and can aid in quantifying human health risk. More specifically, epidemiology compares disease rates in an exposed group of people to those in

an unexposed group. For example, one can examine asthma rates in children in a community living near a highway *vs.* those who live farther away. Epidemiological techniques can also take into account other factors that may influence an exposure or disease, such as age, weight, and smoking status, to determine if an exposure and a disease are linked. For example, it can answer the question: after accounting for whether children's parents smoke, is there

still an association between highway proximity and asthma?

There are several types of epidemiological study designs, and the type of question being asked dictates which epidemiological study design should be used. Three of the major study designs are described in the figure. Cohort studies follow exposed and non-exposed people over time to determine if disease rates differ in the two groups. Case-control studies determine whether exposures in the past differ in diseased and non-diseased people. In a cross-sectional study, exposures and disease status are determined simultaneously in a group of individuals – it is a picture at a precise moment in time. Cohort studies are most often used in risk assessments

*One of the primary advantages of epidemiology is that it measures exposures and diseases in people, which makes it unnecessary to extrapolate the results from laboratory animal studies.*

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# Epidemiology and Risk Analysis

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because they frequently have large sample sizes and extensive exposure information. All study designs have several strengths and weaknesses that epidemiologists must consider when designing a study.

There are different metrics available to quantify risk in epidemiology. Study design, ascertainment of exposure, and disease data affect which metric should be used. For example, in cohort studies, risks can be calculated because disease is measured in exposed and non-exposed people. In a case control study, however, exposure (rather than disease) is measured in diseased and non-diseased people, so only odds can be determined. Each metric is a comparison of the risk (or odds) of having a disease in an exposed group to the risk in an unexposed group of individuals. When an unexposed group of individuals is not available for study comparison, which often occurs in occupational studies, risks can be compared to a standard population (*e.g.*, in many occupational studies of dioxin, disease rates in factory workers are compared to those in the countries where the factories are located). If the ratio of risks is very high, then it is likely that the exposure is associated with the disease. If the ratio is approximately equal to 1, then the exposure is not likely to be associated with the disease, and, if it is less than 1, the exposure could actually be associated with a decreased disease risk.

One of the primary advantages of epidemiology is that it measures exposures and diseases in people, which makes it unnecessary to extrapolate the results from laboratory animal studies. In addition, several epidemiological study designs can address whether disease severity increases with higher exposures, whether exposure actually occurred before the disease, the strength of the association, and whether results are consistent with previous studies.

There are aspects of epidemiology that make the science challenging when attempting to answer certain questions. For example, it is often difficult to measure exposures in people (*e.g.*, there are currently very few, if any, reliable tools to measure occupational exposures to nano-sized materials). In addition, while one can expose animals or cells to very high doses of chemicals, it is unethical to dose humans with chemicals that could cause harm, and often it is difficult to find study subjects that have received a high enough exposure level to measure.

Epidemiology studies can rarely address biological plausibility, so studies (typically in animals) that examine biological pathways are needed to determine a mode of action. It should be noted, however, that these mode-of-action studies are not sufficient to determine causality in humans because a phenomenon observed in a test tube or an animal will not necessarily occur in humans. Thus, results from both epidemiological and laboratory-based studies are needed to address whether a chemical can cause a disease and if it can do so in humans.

*The author can be reached at [jgoodman@gradientcorp.com](mailto:jgoodman@gradientcorp.com).*

## EPIDEMIOLOGY STUDY DESIGNS

Study Type	Cohort	Case-Control	Cross-Sectional
Disease Ascertainment	Prospective or Retrospective	Retrospective	Retrospective
Risk Assessment	RR, SMR, SIR	OR	RR
Strengths	<ul style="list-style-type: none"> <li>• Good for rare exposures</li> <li>• Less bias in risk factor data</li> <li>• Can measure incidence and risk</li> </ul>	<ul style="list-style-type: none"> <li>• Good for rare diseases</li> <li>• Relatively inexpensive</li> <li>• Less time and fewer people</li> </ul>	<ul style="list-style-type: none"> <li>• Relatively inexpensive</li> <li>• Less time and fewer people</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>• Large number of people</li> <li>• A long time to carry out</li> <li>• Potentially high drop out rate</li> <li>• Methodology changes over time</li> <li>• Expensive</li> </ul>	<ul style="list-style-type: none"> <li>• Can only measure odds ratio</li> <li>• Incomplete information about past events</li> <li>• Subjects may not remember past exposures or risk factors</li> </ul>	<ul style="list-style-type: none"> <li>• Most effective for common exposures and diseases</li> <li>• Subjects may not remember past exposures, risk factors, or events</li> </ul>
Examples	<ul style="list-style-type: none"> <li>• Framingham Study of Cardiovascular Disease</li> </ul>	<ul style="list-style-type: none"> <li>• Lung cancer and smoking</li> <li>• Mesothelioma and asbestos</li> </ul>	<ul style="list-style-type: none"> <li>• Mortality and air pollution</li> </ul>

RR: Relative Risk, the measure of risk in an exposed population compared to the risk in a non-exposed group.

SMR: Standardized Mortality Ratio, the ratio of observed deaths to expected deaths in a population.

SIR: Standardized Incidence Ratio, the ratio of observed disease incidence to expected disease incidence in a population.

OR: Odds Ratio, the odds of having a disease with a risk factor present compared to the odds of having a disease with a risk factor absent.

# When Are Disease Clusters Real?

By Lorenz Rhomberg, Ph.D. and Todd Hudson, MSPH

*The apparent clustering of diseases, especially cancer, can usually be explained by random occurrence.*

A cancer cluster is the apparent occurrence in a small geographic area of more cancer cases than would be expected just by chance. Often such clusters are reported by concerned community members, who, finding an unsettling number of cancer cases in their area, fear that some local contaminant or hazard is responsible, since so many nearby cases “can’t just be coincidence.” Public health and environmental agencies investigate such clusters by seeking possible causes and also by analyzing whether what at first seems extraordinary

**Cancer is a more common disease than is widely realized, and when people begin to tally up local cases, counts that are typical of most communities appear unusual.**

is really beyond what might be expected. In the great majority of such cases, no particular causative agent is found, and, moreover, closer scrutiny often reveals that coincidence is the likely explanation.

There are several tools that can be used to determine if a perceived cluster is attributable to chance or if the individual cases are actually related. The Centers for Disease Control and Prevention (CDC) has developed a systematic stepwise process to evaluate potential clusters (EPRI, 1992; CDC, 1990). The most common outcome reveals that local cancer rates are not actually unusual (Thun and Sinks, 2004). Cancer is a more common

disease than is widely realized, and when people begin to tally up local cases, counts that are typical of most communities appear unusual. When an atypically large number of cancers is indeed found, investigators examine whether the cancers comprise cases of related diseases (*e.g.*, all lymphatic cancers). Individual carcinogens typically cause particular forms of cancer; thus, a collection of disparate cancers in several different organs is unlikely to have a common cause. If a set of similar cancers is identified, statistical descriptions of the patterns of closeness of cases geographically and across time can help discriminate patterns that tend to arise by chance from those that have specific local causes. Finally, epidemiologic studies can seek common patterns of exposure, lifestyle, or other factors among those affected to see if a potential underlying cause can be identified. Different demographic groups have different rates of occurrence for many cancers; the nonrandom way that people sort out their living places can lead to geographic differences in cancer rates that have nothing to do with local exposures. For instance, affluent neighborhoods may have higher breast cancer incidence rates only because affluence is a risk factor for breast cancer.

Even a random scattering of spontaneous background cancers across a widespread population will lead to some cases being especially near others in one region or other, completely unrelated to any local cause (see figure). Nonetheless, if one is in the middle of such a chance concentration, it may look locally like a cluster and may prompt people to ask, “What is special about this place that makes the rate high?” In fact, nothing may be special, but the apparent clustering will prompt local people

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## CLUSTERS IN A RANDOM DATASET



*This is a hypothetical distribution of cancer cases in Cambridge, MA derived from a random point set. Even though this is random, statistically significant clusters can be found.*

# Use of Human Data in Risk Assessments

By Ari Schoen Lewis, M.S.

*Several types of human data, including epidemiology studies, biomonitoring data, and gene expression, can provide important insights into risk assessment.*

Understanding the risks humans face every day from chemicals in their environment has many challenges. While animal studies offer a convenient way to assess the toxic effects of chemical exposures in a controlled environment, biological differences among species, as well as high doses used in animal

***Basing risk assessments on early, toxicologically relevant consequences of chemical exposure can increase both the sensitivity and specificity of a risk evaluation, leading to a more reliable interpretation of potential human risk.***

studies, are important sources of uncertainty in extrapolating animal studies to humans for purposes of risk assessment.

Using human data to assess human risk offers certain advantages over using animal studies, but there is a trade-off.

When we exchange

our rat subjects for humans, we gain greater insight into the toxicological relevance of exposures. But because we cannot administer doses of chemicals to humans, particularly for longer-term studies, exposure estimates in human studies may be highly uncertain. Additionally, human studies also must account for other environmental exposures, as well as the influence of dietary and lifestyle factors. The uncertainties associated with using human data are reflected in the risk assessment of inorganic arsenic. Arsenic is unique in that several populations around the world are exposed to high amounts of inorganic arsenic in their drinking water supply. Efforts to use studies of populations outside the U.S. (and particularly in Taiwan) to assess risk in the U.S. have been hampered by an inability to precisely define arsenic exposures, co-exposures to other cancer causing agents, and nutritional and socioeconomic differences between the Taiwanese and U.S. populations.

New developments are enhancing the ability to use human data for risk assessment. For example, on a nationwide basis, the Centers for Disease Control and Prevention now monitors over 100 chemicals in human serum and urine. This type of approach allows for more precise exposure estimates, and thus may one day enhance the reliability of epidemiological studies. It is also possible to look beyond actual chemical exposure and, instead, examine a resulting biological effect of a chemical (called a biomarker of effect); an example would include induction of

an enzyme on the causal pathway of a disease process. Basing risk assessments on early, toxicologically relevant consequences of chemical exposure can increase both the sensitivity and specificity of a risk evaluation, leading to a more reliable interpretation of potential human risk.

Another important new area where human data may refine risk assessment is the identification of specific genes that enhance or diminish individual susceptibility to chemically-induced health effects. As an example, several genes in humans responsible for arsenic metabolism can exist in alternate forms. New research suggests that arsenic metabolism and subsequent disease incidence may be related to individual-specific gene expression. For example, individuals expressing a specific form of a gene called GSTM1 may be more sensitive to arsenic-induced lung cancer.

Thus, while challenges remain (*e.g.*, the toxicological relevance of a particular biomarker and the identification of key genes that influence human susceptibility), greater reliance on high-quality, relevant human data can be an important tool to reduce uncertainty in human health risk assessment.

*The author can be reached at [alewis@gradientcorp.com](mailto:alewis@gradientcorp.com).*

## BY THE WAY...

**Over a 22-year period, the Centers for Disease Control and Prevention investigated 108 alleged cancer clusters in 29 states and five foreign countries. Even though several types of data collection were used, no clear cause was found for any cluster.**

Source: Caldwell, G.G. 1990. Twenty-two years of cancer cluster investigations at the Centers for Disease Control. *Am. J. Epidemiol.* 132 (Suppl. No. 1): S43(5).

## What's New at Gradient

### Recent Appointments/Promotions

**Tom A. Lewandowski, Christopher M. Long, and Jennifer K. Saxe** have been promoted to the position of Principal Scientist at Gradient Corporation.

**Barbara D. Beck** has been appointed to the Massachusetts Department of Public Health Advisory Committee, Arbovirus Work Group.

**Tom A. Lewandowski** has been elected Councilor (2006-2008) of the Society of Toxicology Ethical, Legal and Social Issues Speciality Section.

**Lorenz R. Rhomberg** was named to the NRC Standing Committee on Risk Assessment Issues and Reviews.

### Recent Articles

**Bowers, T.S. and B.D. Beck.** 2007. Response to comments by Bergdahl, Hornung *et al.*, Jusko *et al.*, and Svendsgaard *et al.* on "What is the meaning of non-linear dose-response relationships between blood lead concentration and IQ?" *Neurotoxicol.* 28:197-201.

**Rhomberg, L.R. and T.A. Lewandowski.** 2006. Methods for identifying a default cross-species scaling factor. *Hum. Ecol. Risk Assess.* 12:1094-1127. Chosen as the journal's Human Health Risk Assessment Paper of the Year.

**Thakali, S.,** H.E. Allen, D.M. Di Toro, A.A. Ponizovsky, C.P. Rooney, F.J. Zhao, and S.P. McGrath. 2006. A Terrestrial Biotic Ligand Model. 1. Development and Application to Cu

and Ni Toxicities to Barley Root Elongation in Soils. *Environ. Sci. Technol.* 40:7085-7093.

**Thakali, S.,** H.E. Allen, D.M. Di Toro, A.A. Ponizovsky, C.P. Rooney, F.J. Zhao, S.P. McGrath, P. Criel, H. Van Eck-out, C. Janssen, K. Oorts, and E. Smolders. 2006. Terrestrial Biotic Ligand Model. 2. Application to Ni and Cu Toxicities to Plants, Invertebrates, and Microbes in Soil. *Environ. Sci. Technol.* 40:7094-7100.

**Valberg, P.A., C.M. Long, and S.N. Sax.** 2006. Integrating studies on carcinogenic risk of carbon black: epidemiology, animal exposures, and mechanism of action. *J. Occup. Environ. Med.* 48(12):1291-1307.

**Valberg, P.A.,** T.E. van Deventer, and M.H. Repacholi. 2007. Workgroup report: Base stations and wireless networks – radiofrequency (RF) exposures and health consequences. *Environ. Health Perspect.* 115:416-424.

**Wait, D.** and C. Ramsey. 2007. The Measurement Process. In *Introduction to Environmental Forensics Second Edition.* (Eds: Murphy B.L. and R.D. Morrison), Academic Press, Burlington, MA, pp. 83-128.

### Recent Awards

A Gradient Corporation 2007 Society of Toxicology Meeting poster won an award for "Top 12" posters in risk assessment: **Teresa S. Bowers** and **Peter A. Valberg.** "Non-Linear Exposure-Response Relationships Between Ambient PM<sub>10</sub> and Daily Mortality."

## When Are Disease Clusters Real?

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to ask the question. Because diseases such as cancer are found everywhere, many geographic units will, by chance alone, have one or another type of cancer that is elevated above statistical significance (Neutra *et al.*, 1992). In such cases, no causative effect can be identified and the momentarily high rates (being due to chance) regress back to typical levels in the future.

Rarely, a cluster is traced to a real local cause. In 1850s London, the clustering of cholera cases led to the discovery of contamination in a single well (EPRI, 1992). Mesothelioma rates 9,000 times normal in a Turkish village were traced to a locally occurring mineral (Neutra, 1990). While epidemiologic research of cluster phenomena should not be discounted, the

large majority of disease clusters are attributable either to misperception or random chance.

*The authors can be reached at [lrhomberg@gradientcorp.com](mailto:lrhomberg@gradientcorp.com) and [thudson@gradientcorp.com](mailto:thudson@gradientcorp.com).*

### References:

Centers for Disease Control and Prevention (CDC). 1990. Guidelines for Investigating Clusters of Health Events. MMWR Recommendations and Reports.

Electric Power Research Institute (EPRI). 1992. Cancer clusters: What do they mean?

Neutra, R.R. 1990. Reviews and commentary: Counterpoint from a cluster buster. *Am. J. Epidemiol.* 132(1):1-8.

Neutra, R., S. Swan, and T. Mack. 1992. Clusters galore: Insights about environmental clusters from probability theory. *Sci. Total Environ.* 127(1-2):187-200.

Thun, M.J. and T. Sinks. 2004. Understanding cancer clusters. *CA Cancer J. Clin.* 54:273-280.

# Guest Editorial: Summarizing Epidemiology Studies: The Meta-Analysis

By James J. Collins, Ph.D.

*Meta-analyses, while useful tools for examining multiple epidemiology studies simultaneously, must be viewed with a healthy dose of skepticism.*

The data derived from occupational epidemiology studies are being used more frequently in regulatory decision-making. While a single epidemiology study can rarely be used for causal assessment, the consistency of findings across several epidemiology studies can provide a powerful test of a causal hypothesis.

*Subtle biases can be introduced in meta-analyses in the process of locating and selecting studies, and often these biases can have important impacts on conclusions.*

Many times, it is difficult for any one person to read and organize all studies on a single chemical because there are so many epidemiology studies with conflicting findings. Thus, regulatory and classification agencies, consulting firms, and industry are relying on reviews of epidemiological research on specific chemicals. There are many ways of summarizing epidemiology studies including systematic reviews, best evidence synthesis, pooled analyses, and meta-analysis. Meta-analysis is most frequently used today because it evaluates consistency of results across studies and provides a quantitative summary. However, meta-analysis, since it is a "study of studies," is subject to several biases – sometimes the same biases in the studies the meta-analysis evaluates. Some meta-analyses deal with these biases better than others, which may explain why two meta-analyses reviewing the same chemical specific literature sometimes reach opposite conclusions.

Subtle biases can be introduced in meta-analyses in the

process of locating and selecting studies, and often these biases can have important impacts on conclusions. For example, most meta-analyses rely only on published studies, but studies with null findings are less likely to get published. Further, studies with findings are often published sooner than studies with null findings. Several methods have been developed to assess publication bias, but not all meta-analyses employ these methods. Selection bias can also be introduced by including only studies written in English. Studies with findings are more likely to be published in English. Few meta-analyses include studies written in languages other than English, thus possibly overestimating the perceived impact of exposures.

Variability in exposure assessment and exposure levels across studies may make it difficult to combine studies in a meta-analysis. Exposure assessment is usually more uncertain in a general population case-control study than in a cohort study, and, often, exposures are lower on average in a case-control than in a cohort study because of low exposure prevalence. Thus, combining case-control and cohort studies in a meta-analysis may obscure variability in exposure assessment.

When there are many epidemiology studies on the health impacts of specific exposures, there are often conflicting findings across studies. Meta-analysis has emerged as a way to summarize a large number of studies and produce information useful for a causal assessment. Often the reader is tempted to accept the conclusions of a meta-analysis as an "objective" summary of the data. However, the limitations of these reviews are many times hidden from the reader. The results of meta-analyses are best viewed like the epidemiology studies that they summarize, with potential limitations which may impact their validity.

*The author is the Epidemiology Director at Dow Chemical Company and can be reached at [jjcollins@dow.com](mailto:jjcollins@dow.com).*

## In the next issue:

*What is REACH?*

*How Do Companies Prepare for REACH?*

*Exposure Scenarios Drive REACH Assessments*

*Guest Editorial: REACH from a Legal Perspective*

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GRADIENT  
**TRENDS**  
Risk Science & Application

*Produced by:*

*Gradient Corporation*

*20 University Road*

*Cambridge, Massachusetts 02138*

*Phone: (617) 395-5000*

*Fax: (617) 395-5001*

*Internet: [trends@gradientcorp.com](mailto:trends@gradientcorp.com)*

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