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Risk Science & Application

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Can GRAS Be Used to Support Dietary Supplements?

By Leslie Beyer, M.S., DABT

The GRAS process may offer an alternative path for dietary supplement manufacturers to increase their options and regulatory certainty.

The FDA regulates dietary supplements under the Dietary Supplement Health and Education Act (DSHEA), which defines new dietary ingredients (NDIs) as ingredients not marketed in the U.S. prior to October 15, 1994. If an ingredient or product that is not already registered as an NDI is present in food, an NDI notification (NDIN) is required to demonstrate that the ingredient or product is "reasonably likely to be safe" based on the history of use and testing results. NDIN testing requirements generally include a 90-day animal study and a clinical trial. However, another approach may also be taken – establishing the ingredient as "generally recognized as safe" (GRAS).

Key advantages of conducting a GRAS panel are that a scientific consensus is reached, and the ingredient is designated as a food additive…

The GRAS process dates back to the Food Additives Amendment of 1958, which required manufacturers to test new food additives and file an additive petition with the FDA. The FDA would then evaluate the safety information prior to the additive's use. (The 1958 Amendment also designated 700 food substances as GRAS.) Today, manufacturers can submit GRAS notifications to the FDA for approval, or they can conduct a "self-affirmed" GRAS notification in which the manufacturer does not submit a GRAS notification to the FDA but has the findings

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I N S I D E

Letter from the Editors

September 2013

Dear Colleague,

This issue of *Trends* focuses on the topic of risk analysis under the U.S. Food and Drug Administration (FDA). The FDA's 15,000 employees are responsible for ensuring that approximately $1 trillion worth of goods, from tanning beds to apple juice to stents, are safe. The public relies on the FDA to ensure that food is safe, which means that the FDA must ensure that chemicals introduced in the food supply, both intentionally (*e.g.*, food additives) or non-intentionally (*e.g.*, environmental contaminants), do not pose a health concern. The first article focuses on whether or not the GRAS (generally recognized as safe) process can be used to support the safety of dietary supplements. The second article examines the FDA's newly issued regulations on arsenic in apple juice. Our third article examines the emergence of risk assessment in the FDA's regulation of medical devices.

Gradient contributors to this issue include Ms. Leslie Beyer, a Senior Environmental Health Scientist; Ms. Ari Lewis and Dr. Barbara D. Beck, a Principal Scientist and Principal, respectively; and Dr. Christopher Brynczka, a Senior Toxicologist.

In addition, Mr. Paul D. Rubin and Ms. Kristen Klesh, from the law firm Ropes & Gray LLP, join us with a guest editorial focusing on how FDA risk assessments are impacted by the influence of innovative technologies and personalized medicine.

We hope that this issue of *Trends* provides you with insight into these issues.

Yours truly,

Kurt Herman and Chris Long, Sc.D.
kherman@gradientcorp.com clong@gradientcorp.com

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to use, if needed, to defend the product's GRAS status. For both the FDA-affirmed and the self-affirmed GRAS designations, the manufacturer must demonstrate safe use either through a history of use in foods prior to 1958 or through consensus of qualified experts that publicly available scientific information supports safe use (see figure).

In the latter scenario, a GRAS designation requires a scientific panel of outside experts who are qualified by "scientific training and experience" to evaluate the safety of the dietary ingredient (21 CFR §170.36(c)(1)) in the context of using the dietary supplement as specified on the product label (*i.e.*, "under the intended conditions of use as described in the labeling and packaging"). Thus, if the label explicitly says that pregnant women and children under the age of 12 should not use a product, toxicity/safety data for these two groups would not be included in the evaluation.

GRAS evaluations require calculation of total exposure to the food substance, including both consumption in the product for which the evaluation is being conducted, as well as exposures from other products. For example, if analyzing the safety of caffeine in a particular green tea product, the caffeine ingested from that product would be added to the normal daily caffeine ingestion from other sources (*e.g.*, coffee, soft drinks, chocolate). Then, the safety of the total amount of caffeine consumed is evaluated, generally by conducting a literature review.

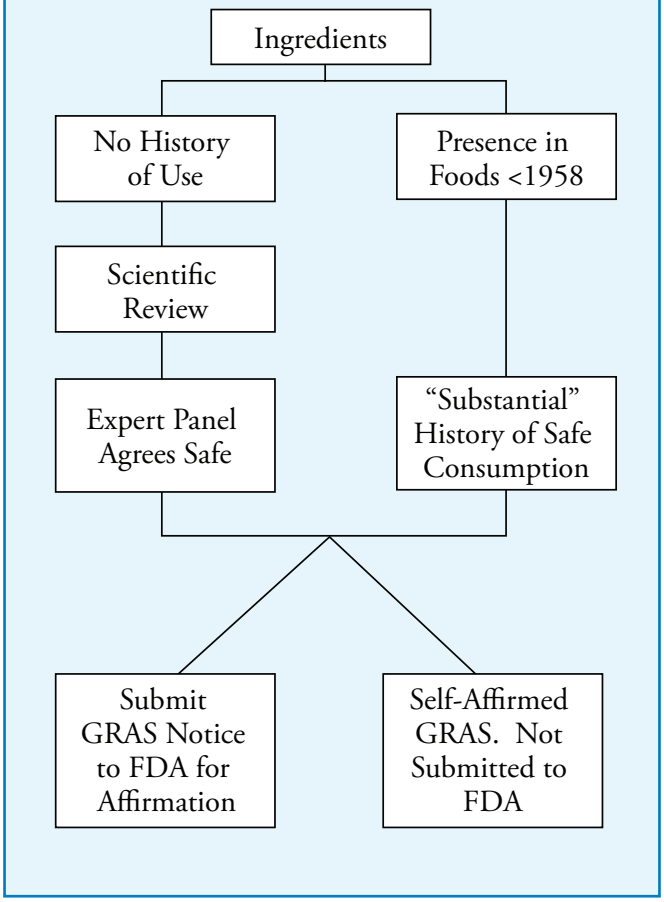
Often the literature on food substances is voluminous (*e.g.*, caffeine, omega 3). To evaluate toxicity efficiently, comprehensive literature searches can be conducted to identify key articles that are 1) current and cover critical endpoints, or 2) comprehensive review articles. Relying on review articles and meta-analyses whenever possible can provide a comprehensive evaluation of toxicity in a timely manner. In addition, key studies can be included that are especially informative due to size, length of follow-up, or scope. Then, this universe of articles can be used to identify the health endpoints of concern (*e.g.*, cardiovascular effects, glucose metabolism, reproductive health, cancer). In-depth evaluation of these endpoints is key to the GRAS process and to choosing members of the GRAS panel, whose expertise should dovetail with the most important health effects.

Key advantages of conducting a GRAS panel are that a scientific consensus is reached, and the ingredient is designated as a food additive, which is a broader designation than afforded under DSHEA. Under DSHEA, if an NDIN is approved, it only applies to a particular dietary supplement. If the product is subsequently used as a food additive, an additional evaluation under GRAS would be needed. Conversely, if a substance is GRAS and used in a dietary supplement, an NDI evaluation may not be required. In addition, the GRAS process is relatively well defined, and consequently, GRAS notifications have greater predictability and a better success rate than NDI submissions, which only have a 25-30% success rate.

So, although GRAS is a safety review process for food additives, it may also be a good option for dietary supplement manufacturers, particularly if the ingredient may be used as a food additive at a later date. The GRAS process not only offers greater regulatory certainty and flexibility to dietary supplement manufacturers, but its "expert panel" review process is a model for applying scientific consensus to analyzing risk for informed decision-making.

The author can be reached at lbeyer@gradientcorp.com.

GRAS Process for Food Ingredients



FDA Takes a Bite Out of Arsenic in Food

By Ari Lewis, M.S., and Barbara D. Beck, Ph.D., DABT, FATS

While the food industry reacts to new FDA regulations on acceptable levels of inorganic arsenic (InAs) in apple juice, the broader issue of InAs toxicity will not be quickly or easily addressed.

The FDA's role in the regulation of food contaminants is front and center as it prepares to issue regulations on acceptable levels of inorganic arsenic (InAs) in various types of food. The presence of InAs in food is nothing new, but public awareness of it is. InAs exists naturally in water, soil, and rock, which means it will find its way into the plants and animals we eat, even in areas with no anthropogenic sources of arsenic. Although the presence of InAs in food is certainly no "news flash," several recent media reports on InAs in food (*e.g.*, fruit juice, rice, and chicken) have intensified the public scrutiny.

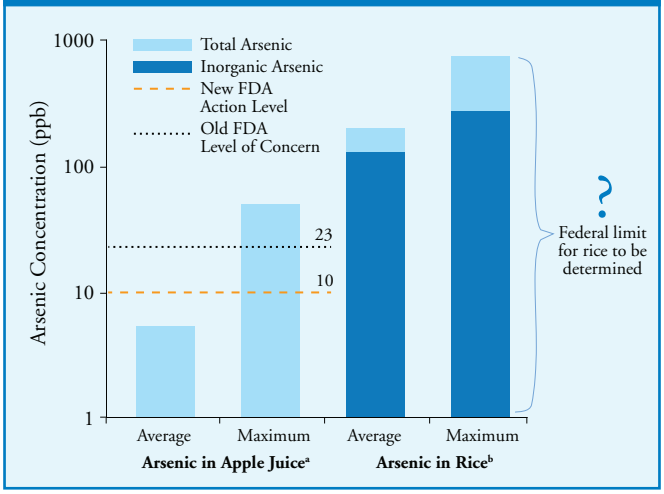
Regulatory assessments of InAs have a long, controversial history.

The FDA has slowly waded into the waters of arsenic regulation for good reason. Regulatory assessments of InAs have a long, controversial history. At sufficient doses, ingestion of InAs can cause both cancer and noncancer effects. Previous InAs assessments led by the U.S. Environmental Protection Agency (EPA) have assumed that InAs has a linear low-dose response such that any exposure to InAs increases cancer risk. Under this linearity assumption, naturally occurring background InAs would result in a risk above the generally accepted cancer risk range of one in a million to one in ten thousand. However, recent toxicological and epidemiological evidence supports a carcinogenic threshold for InAs, indicating that these cancer risk exceedances are not realistic. This aspect of InAs cancer risk assessment has posed a perpetual challenge for the EPA when developing risk-based criteria for soil and water. The challenge it poses for the FDA may be even more formidable given that naturally-occurring InAs in the diet cannot be eliminated and is consumed by most Americans on a daily basis.

Adding to the complexity of the FDA's task to address dietary InAs is that the EPA is in the process of re-evaluating the toxicity of InAs. Based on recent scientific developments (*e.g.*, new studies that inform the mode of action and low-dose responses to InAs), it is clear that critical scientific issues regarding InAs toxicity require careful consideration. Because of the complexity of the toxicological issues involved, the EPA's assessment is being reviewed by a National Research Council panel that will undoubtedly influence the assessment. The EPA's timeline for completing its assessment remains several years out.

Unfortunately, the FDA does not have the option of waiting for the EPA arsenic assessment. The public (and Congress [H.R. 6509]) have demanded that the FDA address the issue expeditiously. In response, the FDA has just recently [July 11, 2013] issued a draft "action level" of 10 µg/L for the long-term consumption of InAs in apple juice. This level replaces a previously developed "level of concern" of 23 µg/L that was based on noncancer effects associated with short-term exposure. Interestingly, the new action level is identical to the limit for InAs in bottled water set by the FDA in 2005 (which is based on the Maximum Contaminant Level [MCL] for arsenic), even though that water limit was derived using different data and exposure assumptions. While many aspects of the apple juice risk assessment are novel, it follows the previous EPA assessments in assuming a linear, no threshold dose response. However, recognizing that the EPA is currently evaluating technical issues related to InAs, including low-dose extrapolation assumptions, the FDA has stated that it "will review new significant scientific findings as they become available."

Arsenic in Rice and Apple Juice *vs.* Regulatory Standards



a - Includes concentrate and finished juice products from FDA study. FDA reports Total As only (but has concluded that "most" is inorganic).
b - Includes domestic and international rice samples from FDA preliminary data.

The FDA's apple juice risk assessment process, including what will transpire during the public comment period, will undoubtedly lay the groundwork for the next item on the menu: rice. Arsenic exposure from rice is more substantial than from apple juice and affects a much larger portion of the population. Although the timing of this assessment is unclear, the FDA's decision could have far-reaching implications for rice growers and importers, and has the potential to affect the food choices of millions of Americans.

The authors can be reached at alewis@gradientcorp.com and bbeck@gradientcorp.com.

Medical Device Risk Assessment

By Christopher Brynczka, Ph.D., DABT

New FDA and ISO guidance is bringing needed clarity to the still emerging field of risk assessment for medical devices.

Compared to the 75-year history of medical device regulation in the U.S. following passage of the Food, Drug, and Cosmetic Act, risk assessment approaches for medical devices have only been prescribed for a relatively short period of time. Arguably, risk assessment has only gained application for medical devices since the 2002 publication of ISO 10993-17, which established guidelines for the calculation of allowable limits for leachable substances. Risk assessment and hazard characterization were brought to the forefront in 2009 by ISO 10993-1, where concepts promoting the development of medical devices within a risk management framework were introduced. Most recently, the FDA introduced draft guidance in April 2013, which engrains hazard assessment, risk assessment, and risk management into the figurative medical device lexicon. This current emphasis on toxicological risk assessment in device development arguably signals the maturation of the field.

This current emphasis on toxicological risk assessment in device development arguably signals the maturation of the field.

The sanctioning of risk assessment by ISO and the FDA influences the strategy of device development beyond the borders of the U.S. The ISO 10993 series of guidance documents are challenged with the unenviable task of harmonizing the criteria for medical device development in the world's major markets, including the U.S. The 2013 FDA draft guidance, referenced above, clarifies the agency's position on the applicability of 10993-1 in the U.S. and adds testing requirements beyond those specified in the ISO guidance; in doing so, it may become the *de facto* standard for device companies seeking access to the U.S. market. The guidance emphasizes the use of hazard and risk assessment as tools applied to understand the clinical implications of chemical exposures. Specific areas identified for toxicological evaluation include material selection and characterization, review of chemical characterization to support claims of substantial equivalence, assessment of chemical exposure in the context of failure analysis, chemical carcinogenicity assessment, assessment of potentially toxic polymer additives, and assessment of device formulation or manufacturing changes. Notably, the guidance specifically identifies incorporated color additives and pigments for evaluation by risk assessment, therefore signaling that regulatory scrutiny of these additives may be expected.

The characterization of chemical exposure from a device is prerequisite for the risk assessment process, and model solvents and exaggerated incubation conditions are commonly used to define the chemicals migrating from device polymers ("extractables" and "leachables"). However, challenges remain in the identification of detected chemicals, which in turn can become a significant toxicological hurdle (*i.e.*, how to identify a chemical's toxicity if its identity is unknown). To meet these regulatory challenges, new risk assessment practices and analytical techniques are under development. These techniques include development of Thresholds of Toxicological Concern (TTC) for parenteral and inhalation exposures, *in silico* identification of chemical surrogates, and the application of Analytical Evaluation Thresholds (AET). Combined, these and other tools enable the qualification and assessment of data-poor compounds and are instrumental to meet the regulatory mandate for characterization and evaluation of medical device chemical exposures.

Thus, while risk assessment has a relatively short history within the context of medical device development, recent FDA guidance indicates the practice will continue to develop as an indispensable tool for the evaluation of medical device safety.

The author can be reached at cbrynczka@gradientcorp.com.

References:

International Organization for Standardization (ISO). 2002. Biological Evaluation of Medical Devices – Part 17: Establishment of Allowable Limits for Leachable Substances. ISO 10993-17.

International Organization for Standardization (ISO). 2009. Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Framework. ISO 10993-1.

U.S. Food and Drug Administration. 2013. Draft Guidance for Industry and Food and Drug Administration Staff. Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing. April.

By The Way...

According to the FDA, 10% of medicines in the world are counterfeited.

Source: Marini, R.D., *et al*. 2010. Analytical Tools to Fight Against Counterfeit Medicines. *Chimica Oggi/Chemistry Today.* 28(5):10-14.

What's New at Gradient

Awards and Announcements

Lorenz Rhomberg has been appointed to the Editorial Board of the journal *Risk Analysis.*

Barbara D. Beck was reappointed as a Visiting Scientist in the Molecular and Integrative Physiological Sciences Program in the Department of Environmental Health at the Harvard School of Public Health.

Tim Verslycke was elected president of North Atlantic Chapter of SETAC for 2013-2014.

Leslie Beyer served as a scientific reviewer of the 2013 American Herbal Products Association's (AHPA) *Botanical Safety Handbook,* Second Edition.

Publications

Long, C.M., **M.A. Nascarella**, and **P.A. Valberg**. 2013. Carbon black versus black carbon and other airborne materials containing elemental carbon: Physical and chemical distinctions. *Environ. Pollut.* DOI:10.1016/j.envpol.2013.06.009.

Prueitt, R.L., **L.R. Rhomberg**, and **J.E. Goodman**. 2013. Hypothesis-based weight-of-evidence evaluation of the human carcinogenicity of toluene diisocyanate. *Crit. Rev. Toxicol.* 43(5):391-435.

Upcoming Presentations

Las Vegas, NV. **Sept. 26-27, 2013**. Minor Metals Americas Conference.

- **D.B. Mayfield**. "Environmental Regulations for Strategic Metals: How Can the Industry Navigate These Challenges?"

San Antonio, TX. **Nov. 12-14, 2013**. International Petroleum Environmental Conference (IPEC).

- **S.A. Flewelling** and **M.P. Tymchak**. "Hydraulic Fracture Height Limits and Fault Interactions in Tight Oil and Gas Formations."
- **M.P. Tymchak** and **S.A. Flewelling**. "A Comparison of Recent Seismic Events Proximate to Underground Injection Wells."
- **M. Sharma** and **S.A. Flewelling**. "Human Health Risk Evaluation for Hydraulic Fracturing Fluid Additives."
- **J.M. Kneeland** and **E.L. Butler**. "Hydraulic Fracturing Fluid Forensics: Potentials and Pitfalls."
- **C.M. Long** and **P.A. Valberg**. "Recent Developments Related to the Health Effects of Diesel Exhaust (DE): Implications for Hydraulic Fracturing and Oil & Gas Development."
- **E.L. Butler** and **C.B. Tuit**. "Multiple Forensic Approaches Used to Evaluate Claims Against a Refinery That Had Been Closed More Than 30 Years."

Nashville, TN. **Nov. 21, 2013**. SETAC North America Annual Conference.

- **J.M. Kneeland**, **W.T. Mehler**, **A.S. Lewis**, and **M. Sharma**. "Strategies for Registering Polymers of Low Concern in Multiple International Markets."
- **W.T. Mehler**, **J.M. Kneeland**, **A.S. Lewis**, and **M. Sharma**. "Importation of Industrial Chemicals in Emerging Markets: A Unified Strategy for Data Compilation and Generation."
- **T.A. Verslycke**. "Validation of the Mysid Two-Generation and Copepod Lifecycle Assays for the Regulatory Testing of Endocrine Active Compounds."
- **J.A. Taboney**. "Relative Contribution of Inhalation of Lead Soil Particulate Matter to Gardener's Lead Exposure."

Baltimore, MD. **Dec. 8-11, 2013**. Society for Risk Analysis Annual Meeting.

- **J.E. Goodman** and **L.R. Rhomberg.** "Bradford Hill Viewpoints and Hypothesis-Based Weight of Evidence."
- **J.E. Goodman**, **S.N. Sax**, S. Thakali, and **L.A. Beyer**. "Rethinking Meta-analysis: Applications for Air Pollution Data and Beyond."
- **J.E. Goodman**, **R.L. Prueitt**, **S.N. Sax**, **L. Bailey**, and **L.R. Rhomberg**. "Incorporation of Weight-of-Evidence Best Practices in the National Ambient Air Quality Standards Review Process."
- **J.C. Lemay**, **R.L. Prueitt**, **M.L. Hixon**, and **J.E. Goodman**. "Distinguishing Between Risks and Hazards: A Case Study of Bisphenol A."
- **L.R. Rhomberg**. "Challenges and Approaches for Evidence Integration Regarding Endocrine Disruption, Exemplified by the Case of Bisphenol A."
- **L.R. Rhomberg**. "Using Existing Study Data or Methodologies from Epidemiology and Toxicology to Evaluate Diverse Stressors."
- **L.R. Rhomberg**, **L. Bailey**, and **M.A. Nascarella**. "Hypothesis-Based Weight-of-Evidence and Dose-Response Evaluation for Naphthalene Carcinogenicity."
- **L.R. Rhomberg** and **L. Bailey**. "Hypothesis-Based Weight of Evidence: An Approach to Assessing Causation and its Application to Regulatory Toxicology."
- **S.N. Sax**, **R.L. Prueitt**, and **J.E. Goodman**. "Weight-of-Evidence Evaluation of Short-Term Ozone Exposure and Cardiovascular Effects."

Guest Editorial: The Influence of Innovative Technologies and Personalized Medicine on FDA Risk Assessments

By Paul D. Rubin and Kristen Klesh

The FDA's new approach to companion diagnostics and OTC switch applications is good news for medical device and drug manufacturers working in the personalized medicine arena.

New technologies have the ability to significantly alter the risk-benefit ratio for drugs and devices, enabling the U.S. Food and Drug Administration (FDA) to approve products that otherwise may have been denied approval in the absence of technological advancements. In the context of personalized medicine, for example, technological advancements may enable companies to identify (*via* genetic testing, disease profiles, and/or other identification criteria) those individuals susceptible to adverse events and/or limited efficacy.

...FDA may be heralding a paradigm shift that will result in significant public health benefits.

The FDA's openness to new technologies, potentially forging a paradigm shift based upon patient-centered therapy and personalized medicine concepts, is exemplified by the recent FDA developments associated with companion diagnostics and over the counter (OTC) switch applications.

The FDA has demonstrated an increased willingness to consider companion diagnostics (CDx) as part of the drug approval process. A CDx is a biomarker that provides biological and/or clinical information that enables better decision-making regarding the development and use of a potential drug therapy by improving the risk-benefit ratio. While CDx have long been used by drug manufacturers during drug development, in recent years the FDA has been prioritizing the development of CDx that may be used post-approval. In fact, the FDA has indicated that approval for certain drugs *requires* the use of an approved or cleared *in vitro* diagnostic (IVD) companion device. Shortly after issuing its 2011 Draft Guidance on *In Vitro* Companion Diagnostics, for example, the FDA simultaneously approved two drugs along with an IVD companion device, suggesting that use of a CDx can support approval for certain drugs that may not have otherwise survived the FDA's risk assessment process. For example, the FDA approved Pfizer's Xalkori with a CDx after the product demonstrated improvement of 50% and 61% in patients with the ALK-positive gene, while previous studies showed only 10% response rates to chemotherapies in patients that were not tested for the gene.

In 2012, the FDA announced the NSURE program in an effort to increase the number of drugs available OTC by improving consumer self-selection. The FDA's goal is to address the under-treatment of common diseases or conditions by allowing prescription drugs to be available OTC *via* use of innovative technologies or other conditions of safe use. The FDA indicated that innovative technologies may help mitigate OTC switch risks by targeting an appropriate patient population. For example, the agency stated that in the context of OTC switch applications, kiosks in pharmacies, questionnaires on the Internet, and diagnostic testing may help consumers diagnose a health condition, select a drug product, and interpret drug warnings.

Under the NSURE paradigm, the FDA has suggested that the risk-benefit ratio may be fundamentally altered *via* use of innovative technologies intended to ensure appropriate consumer self-selection. By considering innovative technologies, the FDA may be willing to approve OTC switch applications that previously may have been incapable of being approved.

Drug and device companies should carefully monitor these, and similar, developments that may fundamentally alter the FDA's approach with regard to risk assessments. By embracing new technologies that improve the risk-benefit ratio, the FDA may be heralding a paradigm shift that will result in significant public health benefits.

Mr. Rubin is a partner, and Ms. Klesh an associate, in the Washington D.C. office of Ropes & Gray LLP. They may be reached at paul.rubin@ropesgray.com or kristen.klesh@ropesgray.com.

References:

U.S. FDA. 2011. Guidance for Industry and FDA Staff – In Vitro Companion Diagnostic Devices. Accessed at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm. July.

Gradient
20 University Road
Cambridge, Massachusetts 02138
(617) 395-5000
trends@gradientcorp.com
www.gradientcorp.com

The next issue will focus on: *International Environmental Issues*

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