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### Do GST Polymorphisms Modulate the Frequency of Chromosomal Aberrations in Healthy Subjects?

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Rossi et al. (2009) described an association between chromosomal aberration (CA) frequency and cancer risk in a case-control study on 107 cancer cases and 291 controls, whereby they observed no modifying effect of polymorphisms in glutathione S-transferase M1 (*GSTM1*) and *GSTT1*.

In our studies of 488 healthy individuals who shared the same environmental exposure in Slovakia and the Czech Republic, we observed a CA frequency of  $2.35 \pm 1.73$  (mean  $\pm$  SD) (Halasova et al. 2007; Musak et al. 2008; Naccarati et al. 2006; Slyskova et al. 2007; Vodicka et al. 2001, 2004a, 2004b). The frequencies (mean  $\pm$  SD) for chromatid-type aberrations (CTA) and chromosome-type aberrations (CSA) were  $1.22 \pm 1.21$  and  $1.15 \pm 1.35$ , respectively. By analyzing modulating effects of genetic polymorphisms in *GSTT1*, *GSTM1*, and *GSTP1* on CAs, CTAs, and CSAs (Table 1), we found no significant association between chromosomal damage and any of the studied polymorphisms. The results were further confirmed by logistic regression: for the *GSTT1* null genotype, odds ratio (OR) = 1.35 [95% confidence interval (CI), 0.79–2.32;  $p = 0.27$ ]; for the *GSTM1* genotype, OR = 1.09 [95% CI, 0.74–1.62;  $p = 0.65$ ]; and for a variant *GSTP1* Val105Val genotype, OR = 0.83 [95% CI, 0.55–1.24;  $p = 0.36$ ]. These data on a larger healthy population [previously published separately by Halasova et al. (2007), Musak et al. (2008), Naccarati et al. (2006), Slyskova et al. (2007), and Vodicka et al. (2001, 2004a, 2004b)] confirm the findings of Rossi et al. (2009) regarding *GSTM1* and *GSTT1* polymorphisms. Additionally, in our

reanalysis, we did not observe any modulating effect of *GSTP1* polymorphism on CA frequency. However, the modulating role of *GST* polymorphisms may not be excluded, particularly in interaction with heavy occupational exposure. In our study exploring chromosomal damage in tire-plant workers (Musak et al. 2008), CAs were significantly higher in subjects with *GSTT1*-null than in those with *GSTT1*-plus genotypes, particularly in association with smoking.

In the past decade, CAs have been accepted as a predictive marker of cancer (Hagmar et al. 2004), particularly for colorectal and lung cancers (Boffetta et al. 2007; Norppa et al. 2006). Nevertheless, these studies, as well as the study of Rossi et al. (2009) may have limitations: For example, cohorts were recruited in various regions with different lifestyle and environmental backgrounds, and different laboratories were involved in processing and scoring the samples over many years. In earlier studies, virtually no data on individual susceptibility were available because of the lack of DNA for molecular analysis.

The data on CAs presented here were obtained on healthy subjects from a homogeneous region with fairly similar socioeconomic background. The analysis of CAs reported in these studies (Halasova et al. 2007; Musak et al. 2008; Naccarati et al. 2006; Slyskova et al. 2007; Vodicka et al. 2001, 2004a, 2004b) were performed in two laboratories, using the same protocol and the same scoring criteria with regular slide exchanges to minimize interlaboratory and interscorer differences. Also, native DNA from whole-blood samples for molecular genetic studies was collected simultaneously with the samples for cytogenetic investigations.

Future prospective studies regarding CAs and cancer should be designed by taking into account the lifestyle and occupational/

environmental exposures, along with factors of individual susceptibility. Some *GST* polymorphisms may modulate CA frequency through interaction with environmental factors. The next logical step for a confirmation of predictive values of CA frequencies in relation to cancer will be their determination in lymphocytes of cancer patients in association with clinical-pathological characteristics.

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**Pavel Vodicka**  
**Alessio Naccarati**  
**Ludmila Vodickova**  
**Veronika Polakova**

Institute of Experimental Medicine  
Academy of Sciences of the Czech Republic  
Prague, Czech Republic  
E-mail: pvodicka@biomed.cas.cz

**Maria Dusinska**  
Slovak Medical University  
Bratislava, Slovak Republic

**Ludovit Musak**  
**Erika Halasova**  
Jessenius Faculty of Medicine  
Martin, Slovak Republic

**Simona Susova**  
**Pavel Soucek**  
National Institute of Public Health  
Prague, Czech Republic

**Kari Hemminki**  
German Cancer Research Center  
Heidelberg, Germany

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**Table 1.** Distribution of analyzed genotypes and CA frequencies.

Genotype	No.	CA			CTA			CSA		
		Mean $\pm$ SD	$\chi^2$	p-Value	Mean $\pm$ SD	$\chi^2$	p-Value	Mean $\pm$ SD	$\chi^2$	p-Value
<i>GSTT1</i> deletion										
Plus	356	2.26 $\pm$ 1.71	1.59	0.21	1.20 $\pm$ 1.21	0.88	0.35	1.11 $\pm$ 1.28	1.01	0.31
Null	74	2.59 $\pm$ 1.84			1.34 $\pm$ 1.29			1.29 $\pm$ 1.47		
<i>GSTM1</i> deletion										
Plus	223	2.28 $\pm$ 1.77	0.43	0.51	1.25 $\pm$ 1.28	0.01	0.90	1.04 $\pm$ 1.32	1.11	0.29
Null	208	2.36 $\pm$ 1.70			1.20 $\pm$ 1.17			1.18 $\pm$ 1.38		
<i>GSTP1</i> Ile105Val										
Ile/Ile	176	2.42 $\pm$ 1.91	2.25	0.33	1.31 $\pm$ 1.38	0.36	0.84	1.12 $\pm$ 1.34	1.27	0.53
Ile/Val	219	2.19 $\pm$ 1.60			1.14 $\pm$ 1.08			1.07 $\pm$ 1.36		
Val/Val	36	2.58 $\pm$ 1.61			1.31 $\pm$ 1.31			1.28 $\pm$ 1.37		

Data, pooled and recalculated from previously published data (Halasova et al. 2007; Musak et al. 2008; Naccarati et al. 2006; Slyskova et al. 2007; Vodicka et al. 2001, 2004a, 2004b), were analyzed by the Kruskal-Wallis test.

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## GST Polymorphisms: Bonassi et al. Respond

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We thank Vodicka et al. for drawing attention to a critical issue—the role of genetic polymorphisms in the induction of chromosomal damage.

First, we would like to clarify that our study (Rossi et al. 2009) was not designed to evaluate the influence of glutathione S-transferase (*GST*) polymorphisms on the frequency of chromosomal aberrations (CAs). Instead, we aimed to identify any possible susceptibility alleles that would increase the strength of the relationship between CAs and risk of cancer in subgroups of genetically variant individuals. The specific purpose of this case–control study explains the relative small size: We planned to obtain data on both CAs and genetic polymorphisms in the same individuals, with all subjects at ages appropriate to allow for an informative follow-up.

The interesting data reported by Vodicka et al. in their letter confirm the extreme heterogeneity of findings when the frequency of chromosome damage is associated with polymorphisms in genes that influence several pathways. In fact, the lack of association in the whole database described by Vodicka et al. contrasts with the significant results reported in exposure-specific subsets, such as the highest frequency of CAs in *GSTT1*-null smokers working in the tire industry (Musak et al. 2008). This interpretation is also supported by the study of Iarmarcovai et al. (2008a), who reviewed 72 population studies reporting a significant effect of *GSTM1*, *EPHX* (microsomal epoxide hydrolase), and *GSTT1* on micronucleus frequency. These authors also reported that the effect observed in specific pathways—such as *ALDH2* in connection to chromosome damage due to alcohol consumption, *BRCA1* and *BRCA2* mutations in breast cancer patients, and *MTHFR* depending on folate levels—was much more pronounced.

A great deal of information about the role of genetic polymorphisms in the induction

of chromosomal damage will stem from genome-wide association studies, when enough resources will be available in the field to explore the genetic determinants of chromosome damage using a whole genome scan. Nevertheless, classical association studies are still valid assuming that specific pathways are identified, possibly *a priori*, linking genotoxic exposure to polymorphisms of genes involved in the correspondent pathway

We would also like to address future strategies for exploring the link between the frequency of chromosome damage and the risk of cancer (and other diseases). We fully agree with Vodicka et al.'s recommendation that possible modifying effects of lifestyle, occupational factors, and genetic polymorphisms be taken into account. However, after finding negative results concerning the role of occupational exposure to genotoxic agents and smoking habit (Bonassi et al. 2000), and polymorphisms of metabolic genes (Rossi et al. 2009), we believe that the remaining factor to be investigated is diet. Many studies have reported on the role of various food items and nutrients as modulators of chromosome stability (Fenech 2007); therefore, this parameter now has top priority, although reliable data are difficult to collect retrospectively.

The other recommendation from Vodicka et al. seems less promising, because measuring the frequency of chromosome damage in cancer patients (besides the classical discussion about whether the damage is a cause or a consequence of the disease) is possibly more a marker of progression than a predictive marker (Iarmarcovai et al. 2008b).

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### Stefano Bonassi

Unit of Clinical and Molecular Epidemiology  
Istituto di Ricovero e Cura a Carattere  
Scientifico San Raffaele Pisana  
Roma, Italy  
E-mail: stefano.bonassi@sanraffaele.it

### Inger-Lise Hansteen

Department of Laboratory Medicine  
Section of Medical Genetics  
Telemark Hospital  
Skien, Norway

### Anna Maria Rossi

### Roberto Barale

Department of Biology  
Pisa University  
Pisa, Italy

### Lisbeth E. Knudsen

Environmental Health  
Institute of Public Health  
University of Copenhagen  
Copenhagen, Denmark

### Hannu Norppa

New Technologies and Risks  
Work Environment Development  
Finnish Institute of Occupational Health  
Helsinki, Finland

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## Green Chemistry: Terminology and Principles

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We are grateful to *Environmental Health Perspectives* for implicitly embracing green chemistry as a field with profound connections to the environmental health sciences. We also commend the efforts of Wilson and Schwarzman (2009) to create greater transparency and accountability around chemicals of concern. We take issue, however, with their approach to key scientific concepts and terminology—specifically their effort to change the definition of “green chemistry.” Precision in terminology is paramount for science to function; all parties to a scientific discussion must share the same set of definitions for knowledge to advance effectively.

In their review, Wilson and Schwarzman (2009) ignored the original and current definition of green chemistry, which for almost two decades has been recognized as a scientific discipline within the field of chemistry.

Defined in the early 1990s by the U.S. Environmental Protection Agency (2009) as “the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances,” green chemistry is now guided by a set of 12 principles (Anastas and Warner 1998) that are used in both research and teaching in chemistry laboratories around the world.

Based on these principles, dozens of universities around the world teach green chemistry as a science. Seven graduate programs offer degrees in green chemistry. Two

established peer-reviewed scientific journals focus specifically on research in green chemistry. The impact factor of the journal *Green Chemistry* (published by the Royal Society of Chemistry) has increased from 2.5 to almost 5 over the past 5 years. More than 1,500 articles on green chemistry have been published in the scientific literature over the past 15 years.

Rather than embracing green chemistry's widely used scientific definition, Wilson and Schwarzman (2009) instead conflate science and policy:

The laws governing the chemical enterprise help define the incentives and disincentives that guide economic behavior in the market .... We use the term green chemistry in this context: as an analytical framework that encompasses both the science of safer chemistry and the laws and policies that will motivate its development and adoption by society.

This conflation brings with it two risks. First, it undermines clarity in scientific communication, something that is especially important as the fields of environmental health and green chemistry attempt to establish cross-disciplinary collaboration. Such collaborations are likely to prove vital for both fields. Second, it saddles the intellectual and scientific enterprise of green chemistry with policy and, potentially, political baggage, as considerations of chemical policies unfold in the political arena.

We are most certainly not arguing that the science of green chemistry should not inform chemical policies. Science and policy will be more effective, however, if political actors do not muddy accepted scientific terminology in service of a political/policy agenda, no matter how noble.

*Karen Peabody O'Brien is executive director of Advancing Green Chemistry, a not-for-profit organization that receives support from several private foundations (listed online at [http://www.AdvancingGreenChemistry.org/AdvancingGreenChemistry/About\\_Us.html](http://www.AdvancingGreenChemistry.org/AdvancingGreenChemistry/About_Us.html)) to support efforts to build the field of green chemistry. J.P. Myers is founder, chief executive officer, and chief scientist for Environmental Health Sciences (EHS), a not-for-profit organization that receives support from several private foundations (listed online at <http://www.environmentalhealthnews.org/about.html>) to support EHS's mission to advance public understanding of environmental health sciences. John Warner is president of Warner Babcock Institute for Green Chemistry, a private company that applies the principles of green chemistry in the synthesis of new materials and the redesign of chemical processes.*

**Karen Peabody O'Brien**

Advancing Green Chemistry  
Charlottesville, Virginia

E-mail: [kpeabrien@embarqmail.com](mailto:kpeabrien@embarqmail.com)

**John Peterson Myers**  
Environmental Health Sciences  
Charlottesville, Virginia

**John Warner**  
Warner Babcock Institute for  
Green Chemistry  
Wilmington, Massachusetts

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## Green Chemistry: Wilson and Schwarzman Respond

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We commend O'Brien, Myers, and Warner for their pioneering work identifying chemical threats to human and ecosystem health and for advancing the field of green chemistry. In our article (Wilson and Schwarzman 2009), we discussed advancing green chemistry as an objective of chemicals policy and described existing policy barriers that, if lifted, would spur the scientific and commercial development of green chemistry. O'Brien et al. recognize that the science of green chemistry has a role in informing chemicals policies. We would add that public policy that accurately reflects current science—and the needs of the chemicals market—is instrumental to the widespread adoption of green chemistry.

Green chemistry's potential is expanded when the science is embedded in a larger context. For example, in an introductory text on green chemistry, Lancaster (2002) stated that

Green chemistry is not a new branch of science, but more a new philosophical approach that underpins all of chemistry and has technological, environmental and societal goals.

Lancaster (2002) pointed out that “over the last ten years, green chemistry has gradually become recognized as both a culture and a methodology for achieving sustainability,” and that the “12 principles of green chemistry help show how this can be achieved” (Lancaster 2002). This book addresses technical aspects of green chemistry while acknowledging the economic, legal, and knowledge barriers to advancing green chemistry.

California has adopted a similarly expansive approach. The state's 2-year old Green Chemistry Initiative is rooted in the

12 principles of green chemistry, and it also embraces a range of tools to ensure the success of green chemistry in society. These include new regulatory strategies, economic incentives, technical assistance, research, and education, with the goal of “launch[ing] a new chemicals framework and a quantum shift in environmental protection” (Adams 2008). These are the same kinds of legislative and regulatory tools that California has used successfully to promote innovation in the energy sector, and which the empirical evidence has identified are the primary drivers for the adoption of cleaner technologies (Nameroff 2004). It is in this context that we see the broad potential of green chemistry.

It is a credit to those who have established the field of green chemistry that multiple interests recognize its value in achieving environmental and economic sustainability, with benefits for worker health, resource conservation, environmental justice, public health, and global warming. As a result, green chemistry is reaching out from a core set of technical principles to inform broad societal goals.

As the field of green chemistry garners increasing attention in the scientific community and in society, it is worth recognizing that the 12 principles of green chemistry will be put to use in many contexts. We welcome the opportunity to join others in engaging with this promising field, with its relationship to the environmental health sciences and its role in effective public policy.

*The authors declare they have no competing financial interests.*

**Michael P. Wilson**  
**Megan R. Schwarzman**

University of California  
Berkeley, California

E-mail: [mpwilson@berkeley.edu](mailto:mpwilson@berkeley.edu)

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*Authors' joint statement: The five authors are currently working on a statement of shared views and goals.*

## Molybdenum Exposure and Semen Quality: How Robust Is the Evidence of an Effect?

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Meeker et al. (2008) reported on associations between blood levels of nine different metals and four aspects of semen quality found in 219 volunteers attending two infertility clinics. Based on the title of their article, it seems that the authors claimed to have found evidence that molybdenum is a male reproductive toxicant. But how robust is the evidence? Meeker et al. (2008) had no primary prior hypotheses, and their study was essentially a “fishing expedition” involving many statistical tests of many possible associations. The authors (Meeker et al. 2008) did note that “some [findings] may be chance findings because of the number of comparisons that were made.” A much stronger statement is appropriate, namely, that it is very likely that some of the findings were chance findings.

The overwhelming majority of study subjects (70%) had blood Mo levels below the study limit of detection of 1 µg/L. If a more sensitive assay method had been used [e.g., the method of Case et al. (2001) with a detection limit of 0.06 µg/L], then a better grouping of subjects could have been used in the data analyses. We also believe the authors made an inappropriate analytical decision. In Table 3 of their article, Meeker et al. (2008) summarized analyses in which dose-dependent associations for each metal were considered in turn while adjusting for age and current smoking. The analysis of associations between Mo concentrations and semen motility were based on data from 147 subjects. The assumption appears to be that 72 (219 – 147) subjects had no useful information to provide on the Mo/sperm motility issue. It would have been more scientifically rigorous to allow the analysis of each semen parameter to make use of data from all study subjects, and not just for the sake of completeness. The current approach has introduced bias into the analysis, because different standards are applied to cases [subjects with the adverse health outcome of interest (e.g. poor sperm concentration)] and controls or referents (subjects without the adverse health outcome). To be concrete, in the analyses of sperm concentrations, cases were allowed to have poor sperm motility, whereas controls were not. The effect of this, in practice, is to load the controls with subjects on high incomes who have never smoked. A more standard analysis involving all study subjects in the analysis of each aspect of sperm quality should have been carried out. Such an analysis would likely have provided very different results to the subset analyses they reported.

In commenting on the linear regression analyses shown in their Table 4, Meeker

et al. (2008) stated that the Mo groups “were associated with suggestive decreasing trends in sperm concentration and morphology.” However, examination of the table shows that neither of the regression coefficients was significantly different from zero (i.e., the blood Mo level had no significant influence on any of the semen quality parameters).

Additional studies would be needed to investigate possible effects in semen quality based on much larger population samples containing a wider range of blood Mo levels.

*The authors are consultants for the International Molybdenum Association.*

### Tom Sorahan

Institute of Occupational and Environmental Medicine  
University of Birmingham  
Birmingham, United Kingdom  
Email: T.M.Sorahan@bham.ac.uk

### Frank M. Sullivan

Toxicologist  
Brighton, United Kingdom

## REFERENCES

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## Molybdenum Exposure and Semen Quality: Meeker et al. Respond

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We appreciate the comments by Sorahan and Sullivan that serve to reiterate the limitations we discussed in our article reporting relationships between metal concentrations in blood and semen quality among 219 men recruited through two Michigan infertility clinics (Meeker et al. 2008). As highlighted in their letter, these limitations included the possibility of chance findings due to multiple comparisons and the sensitivity of the molybdenum assay used, among others. However, dismissing our analysis as a “fishing expedition” is not appropriate, given the animal evidence for adverse effects on male reproductive function in relation to Mo (Institute of Medicine 2001; Jeter and Davis 1954; Lyubimov et al. 2004; Pandey and Singh 2002; Thomas and Moss 1951; Van Niekerk and Van Niekerk 1989; Vyskocil and Viau 1999; Yamaguchi et al. 2007) and other metals. Because evidence exists for numerous metals to be either

harmful or beneficial to male reproduction, and because metals may interact with one another synergistically or antagonistically, we conducted this exploratory study to provide the most comprehensive human data to date on multiple metals and semen quality.

Because our study (Meeker et al. 2008) was the first to assess the relationship between Mo and semen quality in humans, we agree that our findings deserve further consideration and scrutiny through future research. An added impetus for further investigation comes from our recent follow-up analysis in which we reported a strong inverse association between Mo and circulating testosterone in these men, an association that was independent of semen quality (Meeker et al. 2009). Given that testosterone is not strongly predictive of semen quality parameters in this population (correlation coefficients < 0.15) or in other populations (Meeker et al. 2007)—but it does play a vital role in reproduction and other functions in males (e.g., metabolic disorders, bone health, endocrine-related cancers)—our findings suggest that multiple modes of Mo action on male reproduction may be possible and should be investigated.

We considered a number of approaches to model the association between metals in blood and semen quality parameters. In our logistic regression analysis (Meeker et al. 2008), we decided that including only men with all three semen quality parameters above reference values (i.e., “normal”) in the comparison group would be most appropriate, because the use of a heterogeneous comparison group that also includes men with compromised semen quality (i.e., at least one parameter below reference) may erroneously dilute the association between metals and semen quality parameters (Hauser et al. 2006). Sorahan and Sullivan’s assertion that the use of this more homogenous comparison group, which had normal levels of all three parameters, would somehow “overload” the comparison group with high-income nonsmokers in relation to the below-reference groups is unfounded since these factors were considered in the multivariable analyses. Finally, in response to Sorahan and Sullivan’s comment regarding our Table 4 (Meeker et al. 2008), in small-to medium-sized studies it is common practice to use the term “suggestive” instead of “significant” in reporting associations with *p*-values between 0.05 and 0.15. There are many instances where relationships with a *p*-value just above 0.05 should not be completely disregarded, especially (as in this case) if they are consistent with results from other statistical analysis approaches or with previous (e.g., animal) research.

In conclusion, our findings (Meeker et al. 2008) may have large public health implications, but we agree that our study

has several limitations. Our results need to be replicated in other large human studies, and potential biological mechanisms for the observed associations, and for metal-metal interactions, should be investigated in more detailed molecular epidemiologic, animal, and *in vitro* studies. Research is also needed on important sources, pathways, and routes that result in elevated Mo exposure, whether it stems from ingestion of naturally occurring or industrially related contamination of food and water, intentional ingestion of Mo-containing multivitamin/multimineral supplements, potential multipathway exposure resulting from the use of Mo in flame retardants in building materials or consumer products, or a combination of these and other scenarios. Research comparing the utility of measuring Mo in blood, urine, and/or other matrices as biomarkers of Mo exposure over relevant time periods of interest is also needed.

*The authors declare they have no competing financial interests.*

**John D. Meeker**

Department of Environmental  
Health Sciences  
University of Michigan School of  
Public Health  
Ann Arbor, Michigan  
E-mail: meekerj@umich.edu

**Michael P. Diamond**

Department of Obstetrics and Gynecology  
Wayne State University  
Detroit, Michigan

**Julia J. Wirth**

Department of Epidemiology  
Michigan State University  
East Lansing, Michigan

**REFERENCES**

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# ERRATUM

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**NOTE:** In the letter by O'Brien et al. [Environ Health Perspect 117:A385–386 (2009)], the competing financial interest declaration was incorrect. The correct declaration is as follows:

Karen Peabody O'Brien is executive director of Advancing Green Chemistry, a not-for-profit organization that receives support from several private foundations (listed online at [http://www.AdvancingGreenChemistry.org/AdvancingGreenChemistry/About\\_Us.html](http://www.AdvancingGreenChemistry.org/AdvancingGreenChemistry/About_Us.html)) to support efforts to build the field of green chemistry. J.P. Myers is founder, chief executive officer, and chief scientist for Environmental Health Sciences (EHS), a not-for-profit organization that receives support from several private foundations (listed online at <http://www.environmentalhealthnews.org/about.html>) to support EHS's mission to advance public understanding of environmental health sciences. John Warner is president of Warner Babcock Institute for Green Chemistry, a private company that applies the principles of green chemistry in the synthesis of new materials and the redesign of chemical processes.

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In the letter by Wilson and Schwarzman [Environ Health Perspect 117:A386 (2009)], the last sentence in the first paragraph was incorrect. The corrected sentence is as follows:

We would add that public policy that accurately reflects current science—and the needs of the chemicals market—is instrumental to the widespread adoption of green chemistry.

*EHP* apologizes for the error.

This error has been corrected in the PDF version of this article.