U.S. EPA's (U.S. Environmental Protection Agency) ToxRefDB and ToxCast research programs, including the review of much of the data entered into ToxRefDB. However, Janus's comments do not address the ToxRefDB applications presented in our article, but instead create hypothetical uses of the database and reported data.

For example, in Table 3 of our article (Martin et al. 2009a), we presented multigender, multisite, and multispecies rodent tumorigens in order to provide data in a systematic and computable format for predictive toxicity models incorporating potency values. In contrast, Janus and CropLife America refer to a hypothetical regulatory application of this same animal tumorigenicity data in a ranking system never suggested in our article.

The U.S. EPA has gone to great lengths to make ToxRefDB and its development as transparent as possible. Three manuscripts and data sets have been published to date (Knudsen et al. 2009; Martin et al. 2009a, 2009b), and the standardized vocabulary and a version of the database are available on the ToxRefDB website (U.S. EPA 2008b). We will continue to make every effort to publicly release information from ToxRefDB as it continues to develop.

We recognize the complexity of pathologic progression to cancer. The end point progression scheme we presented (Martin et al. 2009a) included aggregation of proliferative, preneoplastic, and neoplastic lesions for the development of predictive signatures from *in vitro* data coming from the ToxCast research program (U.S. EPA 2008a). This approach is not controversial in the context of predictive toxicology research and is supported by the literature (Cohen and Arnold 2008; Hanahan and Weinberg 2000).

We agree that it is important to incorporate pharmacokinetics and metabolism, including chemical detoxification and activation, into predictive toxicology efforts. However, this issue is outside the scope of our article (Martin et al. 2009a) and is being addressed in other aspects of the ToxCast research program.

Two additional papers on multigenerational reproductive and prenatal developmental toxicity studies in ToxRefDB have been recently published (Knudsen et al. 2009; Martin et al. 2009b), again with the primary goal of providing diverse end points for predictive modeling as part of the ToxCast research program (Dix et al. 2007). Of toxicity end points in ToxRefDB, we are using only those of sufficient quality for predictive modeling, and we are taking care to distinguish between missing versus negative data.

We view ToxRefDB as a valuable resource to the scientific community and one in which the U.S. EPA, stakeholders, and other interested parties can work together to ensure the success of ToxRefDB and the larger ToxCast effort.

The authors declare they have no competing financial interests.

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This response does not necessarily reflect official U.S. EPA policy.

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Nanotechnology-Related Environment, Health, and Safety Research

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We were very interested to read the article by Schmidt (2009) about the increasing number of nanomaterials and their potential effects. We were especially interested in the similarities between carbon nanotubes and chrysotile asbestos fibers. The widespread use of asbestos-like substances with similar putative carcinogenic potential could result in the development of other unexpected types of cancer.

The potential carcinogenic risk of nanomaterials that are structurally similar to asbestos and have been used in many industrial fields in the last few years has been highlighted by Carter (2008). Some studies conducted in animal models suggest that nanomaterials cause free radical–mediated cellular DNA damage and consequently have an asbestos-like carcinogenic action (Poland et al. 2008).

In addition to mesothelioma (the typical cancer index of exposure) or lung cancer, asbestos can cause other types of cancer. On the basis of our clinical experience, we hypothesize that at least a portion of bile ducts cancers (i.e., cholangiocarcinomas) are caused by exposure to this known carcinogenic agent.

From 2002 to 2008 we treated 258 patients with cholangiocarcinoma at our institute. Over the previous year, we carefully interviewed 66 consecutive patients using a standardized questionnaire asking about their exposure to asbestos and other known risk factors linked to bile duct carcinogenesis (Khan et al. 2008). We collected each patient's remote, recent, and occupational clinical history. In addition to the association with known risk factors for the onset of cholangiocarcinoma, we assessed occupational or household exposure to asbestos in 24 patients, 10 of whom did not have other certain risk factors (Table 1; Brandi et al. 2008).

Asbestos fibers cause cancer through chronic inflammation, amplifying the production of oxygen radicals, cytokines, growth factors, and proinflammatory factors responsible for both impaired antioxidant and control cell proliferation and apoptosis mechanisms in target cells (Manning et al. 2002). In contrast with findings for pleural mesothelioma, the association between exposure to asbestos and the development of other tumors, such as gastrointestinal and

Table 1. Characteristics of patients.

Tumor site	No. of patients	Exposure to asbestos		Possible modality of exposure		Certain added risk factors[a]	
		Household	Occupational	Ingestion	Inhalation	Absent	Present
ICC	10	7/10	4/10	7/10	4/10	6/10	4/10
Klatskin tumor	6	3/6	3/6	3/6	3/6	3/6	3/6
Ampulla of Vater	1	1/1	–	1/1	–	1/1	–
Main hepatic bile duct	1	–	1/1	–	1/1	–	1/1
GBC	6	6/6	–	6/6	–	–	6/6

Abbreviations: GBC, gallbladder carcinoma; HCV, hepatitis C virus; ICC: intrahepatic cholangiocarcinoma. Data updated from Brandi et al. (2008).
[a]HCV infection or exposure to chemical substances used in industry, sporadic contact with chemical substances used in farming, alcohol-related liver cirrhosis or gallstones, or ulcerative colitis and primary sclerosing cholangitis.

bile duct cancers, has not been univocally demonstrated (Gamble 1994).

The putative increased risk of bile duct cancer in subjects exposed to asbestos may be due to different mechanisms. The asbestos fibers cross the alveolar barrier by inhalation or penetrate the gastrointestinal mucosa by ingestion. They then reach the interstitial environment and circulatory system through lymphatic vessels and are finally delivered to all tissues, namely the liver and bile ducts (Miserocchi et al. 2008), where they may start a malignant transformation process (Wingren 2004). In addition, asbestos fibers may reach the bile ducts through the papilla of Vater from the intestinal lumen by retrograde reflux, as do bacteria, and remain in the gallbladder for a long time.

In the near future we may have to consider asbestos as another factor accounting for the etiopathogenesis of cholangiocarcinomas that may explain the otherwise mysterious increasing incidence of intrahepatic cholangiocarcinomas in Western countries.

The authors declare they have no competing financial interests.

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Errata

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) 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.

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.

In the article by La Merrill et al. [Environ Health Perspect 117:1414–1419 (2009)], the keys in Figure 3B and Figure 5C should have been in Figure 3C and Figure 5D, respectively. The corrected figures are provided below.

EHP apologizes for the errors.

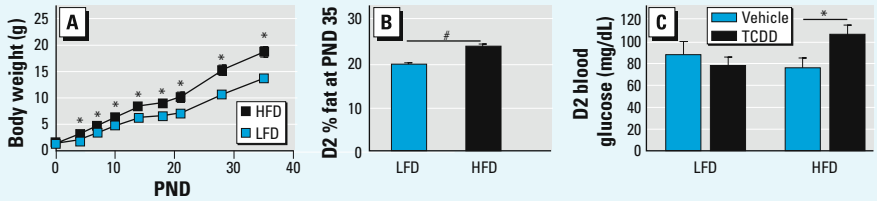

Figure 3. Diet and maternal TCDD exposure effects on body composition and fasting blood glucose. (*A*) HFD increased postnatal D2 body weights (mean ± SE; n = 27–31 at PNDs 0–26 for HFD, and n = 28 at PND35 for LFD). (*B*) HFD (n = 26 mice) increased percent fat at PND35 relative to LFD (mean ± SE; n = 28 mice). (*C*) Fasting blood glucose was increased by HFD and maternal TCDD-treated (n = 5 litters) compared with HFD and maternal vehicle-treated (n = 6 litters) female progeny at PND36 (mean ± SE). Because diet, but not TCDD, changed body weight and percent body fat, these analyses were done on individual D2 mice, with TCDD- and vehicle-treated D2 mice pooled within diet.
*$p < 0.05$. #$p < 0.0001$.

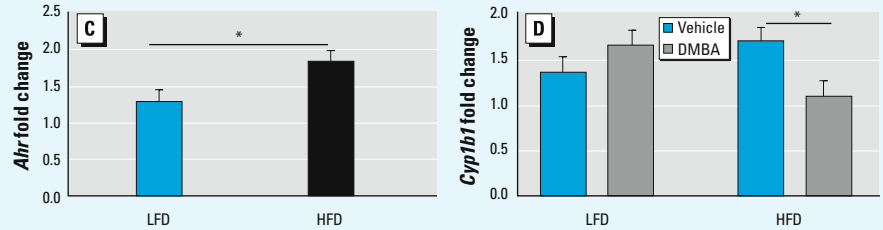

Figure 5. Maternal TCDD exposure and effect of diet on gene expression. Normalized message levels are represented as mean ± SE. (*C*) Induction of *Ahr* was increased by HFD relative to LFD (n = 11 and 10 litters, respectively). Measurements were pooled across TCDD and DMBA groups. (*D*) Induction of *Cyp1b1* by DMBA was decreased compared with vehicle in HFD-fed but not in LFD-fed D2 mice. LFD groups are vehicle (n = 5 litters) and DMBA (n = 5 litters); HFD groups are vehicle (n = 6 litters) and DMBA (n = 5 litters).
*$p < 0.05$.