mission, NICEATM also conducts independent validation studies on new, revised, and alternative test methods, and coordinates international validation studies with its counterparts in Japan, Europe, and Canada (NIEHS 2009).

In 2008, NICEATM and ICCVAM launched a 5-year plan to further reduce, refine, and replace the use of animals in regulatory testing in conjunction with federal agencies and other stakeholders (ICCVAM 2008). The plan seeks to advance alternative test methods of high scientific quality that will continue to protect and advance the health of people, animals, and the environment. The plan emphasizes using new technology to develop predictive systems that will lessen or avoid the need for animals where scientifically feasible.

The NIEHS and NTP support research that may lead to the development of new test methods relevant to regulatory testing. These include the Tox21 collaboration between the NTP, the National Institutes of Health Chemical Genomics Center, and the U.S. Environmental Protection Agency (Schmidt 2009). The Tox21 initiative is the largest *in vitro* toxicology research program ever conducted worldwide and is expected to yield candidate methods and approaches with potential applicability to regulatory testing. Following standardization and validation in consultation with ICCVAM, methods with regulatory applicability will be reviewed by ICCVAM and recommendations forwarded to appropriate agencies.

ICCVAM has been enormously successful in gaining regulatory acceptance of alternative methods (ICCVAM 2010). Gaining regulatory acceptance requires high-quality studies that prove that the alternative test methods will provide the same or better level of protection of workers and consumers as the methods they might replace. The test method must also be shown to be reproducible in different laboratories.

The animal welfare benefits of ICCVAM's work are evidenced by many examples. These include an alternative test for acute oral toxicity that has replaced the LD_{50} test (median lethal dose), which used as many as 200 animals per test, with the Up-and-Down Procedure (UDP), which uses only 7 animals on average per test (NIEHS 2001; Organisation for Economic Co-operation and Development 2008). The UDP and other alternative test methods have profoundly reduced animal use for acute oral toxicity testing, which is conducted to determine the poisoning potential of chemicals and products and is the most commonly conducted safety test worldwide.

Another landmark ICCVAM contribution is the reduction and refinement of animal use for eye-safety testing. ICCVAM evaluated and recommended the first two *in vitro* test methods that can now be used to determine whether substances can cause blindness and other severe eye damage, without the need for live animals (NIEHS 2008). Based on ICCVAM's evaluation, these test methods were adopted as international test guidelines in 2009.

In summary, ICCVAM has demonstrated its effectiveness and value in achieving the regulatory acceptance of test methods that reduce, refine, and replace animal use. Most importantly, by making appropriate science-based decisions, ICCVAM has ensured that such methods will continue to protect the public's health and safety. We expect ICCVAM to serve an increasingly important role in translating research advances into improved test methods that will benefit both people and animals.

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Polyethylene Terephthalate and Endocrine Disruptors

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In the commentary "Polyethylene Terephthalate May Yield Endocrine Disruptors," Sax (2010) theorized that bottles made of polyethylene terephthalate (PET) might leach phthalate ester plasticizers and/or antimony to produce endocrine-disrupting effects. On behalf of the North American producers of PET resin, I have the following comments and corrections.

Phthalate ester plasticizers are not used to manufacture polyethylene terephthalate and never have been. It is not chemically plausible for PET to produce these phthalate esters.

Sax (2010) did suggest that some reports of phthalate esters in PET bottled water containers may have originated from contamination of the bottled water, or from phthalate ester contamination of recycled PET used in manufacturing water and beverage containers. In addition, non-PET components of bottled water containers (e.g., closures) might be another possible source. Whatever the origin of phthalate esters, which could not be identified in any of the studies cited by Sax, it is clearly unreasonable to ascribe PET as the source.

Regarding antimony, Sax noted that Choe et al. (2003) reported antimony chloride as showing high estrogenicity. However, antimony oxides—not antimony chloride—are used as catalysts in the manufacture of PET. Antimony oxides are chemically and toxicologically distinct from antimony chlorides. No study has reported finding toxic amounts of antimony in PET-bottled water or beverages.

PET bottles and containers meet all applicable U.S. and international safety requirements for food contact, and the inert qualities of PET define its preferred use for many food, beverage, and medical applications. Consumers can feel confident about the safety of PET food and beverage containers.

We welcome dialogue with researchers and regulatory agencies on the chemistry and safety of PET resin.

The author is employed as the Executive Director of the PET Resin Association, the industry association representing North American producers of polyethylene terephthalate.

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Sax L. 2010. Polyethylene terephthalate may yield endocrine disruptors. Environ Health Perspect 118:445–448.

Polyethylene Terephthalate: Sax Responds

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In his letter Vasami reminds readers that phthalates are not used in the manufacture of PET. Indeed, I emphasized precisely this point in my commentary (Sax 2010), for example, when I stated that "phthalates are not used as substrates or precursors in the manufacture of PET." Vasami also asserts that "it is not chemically plausible for PET to produce these phthalate esters"; however, I never suggested that virgin PET gives rise to phthalate esters via degradation of PET itself. I did cite multiple studies in which phthalates were recovered from the contents of PET bottles—as contaminants leaching from the PET bottle wall. How did the phthalates come to be there? As I noted, one possibility is that some of the PET used in manufacturing the bottles may have been recycled PET, and some of this recycled PET might have been contaminated with phthalates. Again, as I noted in my commentary, PET is commonly used for bottling a variety of products (e.g. shampoo) that are known to contain phthalates; these phthalates can then sorb into the PET bottle. Other researchers have previously documented that various organic substances readily migrate into PET (e.g., Komolprasert and Lawson 1997). Indeed, previous investigators have documented the presence of phthalates in PET bottles marketed for consumer use (e.g., Kim et al. 1990); Nerín et al. (2000) reported that the concentration of phthalates was much higher in recycled PET material than in virgin PET.

There are good environmental arguments for recycling plastics rather than disposing of them in landfills. The potential for tension between the desire to recycle plastics, on the one hand, and the desire to protect human health, on the other hand, has long been recognized (e.g., Castle 1994). Reconciling these two objectives requires a better understanding of the origin of endocrine disruptors in PET.

Vasami notes that although Choe et al. (2003) reported antimony chloride as showing high estrogenicity, "antimony oxides—not antimony chloride—are used as catalysts in the manufacture of PET." Although Vasami asserts that antimony oxides "are chemically and toxicologically distinct from antimony chlorides," the toxicological literature does not provide strong support for this assertion. Antimony chloride, when combined with water, readily forms antimony oxide (National Research Council 2000), and both antimony chloride and antimony oxide ionize *in vivo*. Merski et al. (2008) reported that when animals were fed ground PET, antimony was recovered from their urine in a dose-dependent fashion. Toxicologically, what seems to matter is the antimony and its oxidation state [trivalent (III) or pentavalent (V)], not the anion (chloride or oxide). Antimony(III) is the ionization state in the antimony oxide used in the production of PET; the same ionization state (III) is found in antimony chloride. Using X-ray spectrometry, Martin et al. (2010) confirmed that the antimony in PET bottle walls is in fact trivalent antimony. The toxicological literature clearly establishes that trivalent antimony is far more toxic to humans than is pentavalent antimony (e.g., Chulay et al. 1988; De Boeck et al. 2003; Phillips and Stanley 2006). Vasami's implication that antimony(III) oxide, when ingested, might be free of the risks demonstrated for antimony(III) chloride, is without evidentiary basis.

Vasami concludes by reminding readers that PET bottles meet all applicable safety requirements. However, he neglects to note that these safety requirements were developed largely in the 1980s and 1990s, when the chief concern about antimony and other metalloids had to do with carcinogenicity (e.g., De Boeck et al. 2003) and organ toxicity (e.g., Poon et al. 1998). The standards were developed based on doses believed to be carcinogenic and/or directly toxic. The ability of inorganic metalloids such as antimony to act as xenoestrogens has only recently been recognized (Darbre 2006). More research is needed to determine whether the regulatory requirements for antimony in foods and beverages should be adjusted in order to minimize the risk of endocrine-disrupting effects.

Certainly there is a paucity of research on the endocrine-disrupting effects of antimony. But surely the remedy for this deficiency is more research, not a stubborn insistence that what we don't know can't hurt us.

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Erratum

In the article "Using National and Local Extant Data to Characterize Environmental Exposures in the National Children's Study: Queens County, New York" by Lioy et al. [Environ Health Perspect 117:1494–1504 (2009)], Shahnaz Alimokhtari was inadvertently omitted as an author. The corrected author names and affiliations are listed below.

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The authors apologize for the error.