

## Are Maternal Thyroid Autoantibodies Generated by PCBs the Missing Link to Impaired Development of the Brain?

In her interesting review addressing endocrine disruption and the developing brain, Colborn (2004) asked rightly for special attention to the role of a disruption of thyroid hormones and thyroid hormone metabolism, which negatively influence early development of the fetal brain. As mechanisms of action, chemicals such as polychlorinated biphenyls (PCBs) were discussed in a dose-related way; the higher the exposure level of the mother, the more problems of brain development will be found in the baby (Colborn 2004). However, this is not always true. Patandin et al. (1999) found a four-point decline in IQ at 4 years of age in relation to maternal PCB levels in the Netherlands. In a follow-up study of Faroese children at 7 years of age, Grandjean et al. (1997) found no relation of PCBs with cognitive impairment; the levels of PCBs were almost 4 times higher in the Faroese population than in the Dutch population (Longnecker et al. 2003).

One explanation of the missing link might be that effects of PCBs are not directly toxic but instead are toxic through immunomodulatory mechanisms in the mother. In a comment on the impact of maternal PCB and dioxin exposure on the neonate's thyroid hormone status, Vulsma (2000) noted that PCBs affect the generation of autoantibodies against thyroid tissue [e.g., thyroid peroxidase antibodies (TPO-Ab)]. In a study in Slovakia, Langer et al. (1998) described an increase in TPO-Ab in relation to PCB exposure. These antibodies do pass through the placenta.

An important risk factor for impaired infant development is a low free thyroxine ( $fT_4$ ) concentration in early pregnancy; particularly at risk are the mothers with low  $fT_4$  and high TPO-Ab titers. These antibodies are found in 10% of (euthyroid) women at 12 weeks' gestation in the Netherlands (Pop et al. 1995, 1999). To my knowledge, none of the studies on effects of PCBs in human pregnancy have reported data on maternal TPO-Ab titers.

If the findings reported by Colborn (2004) can be explained by autoimmune processes that cause low  $fT_4$  in the mother and negatively affect her developing baby, then it seems more logical that prenatal PCB exposure is related to developmental impairment instead of the amount of PCBs transferred by breast milk after birth.

I agree with Colborn (2004) that all women who plan to become pregnant

should be evaluated for thyroid hormone status.

*The author declares she has no competing financial interests.*

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## Maternal Thyroid Autoantibodies: Colborn's Response

I thank Koppe for raising the question of the significance of the presence of increased thyroid peroxidase antibodies (TPO-Ab) during neurodevelopment or even later in life. I have wondered for years why medical practitioners and laboratories do not routinely quantify TPO-Ab in blood screening for thyroid disorders. High priority should be given to learning more about the relationship between the combination of high TPO-Ab and low free thyroxine ( $fT_4$ ), and impaired IQ and psychomotor development and the possible role of foreign substances such as polychlorinated biphenyls (PCBs) in these changes. Although the value of routine antithyroglobin antibody (TG-Ab) testing is being questioned, in future epidemiologic studies looking at the role of PCBs in neurodevelopment perhaps TG-Ab should be included in the design as well. It might prove enlightening to also routinely test for TG-Ab at several research/medical institutions to

continue to explore this immune connection with the thyroid economy. Also, perhaps it is time to explore the nutritional state (protein consumption, quality and quantity of serum proteins) of the mother and her unborn child during gestation, which might contribute to the conflicting findings among the various cohort studies about the role of PCBs in neurodevelopment. In the meantime, until more is understood about neurodevelopmental impairment, I would like to take this opportunity to reinforce the need to routinely test all pregnant women and those planning to become pregnant for  $fT_4$ , free triiodothyronine, thyroid-stimulating hormone, and TPO-Ab. Information such as this would allow for intervention, if needed, to prevent irreversible brain damage.

*The author declares she has no competing financial interests.*

Theo Colborn

The Endocrine Disruption Exchange

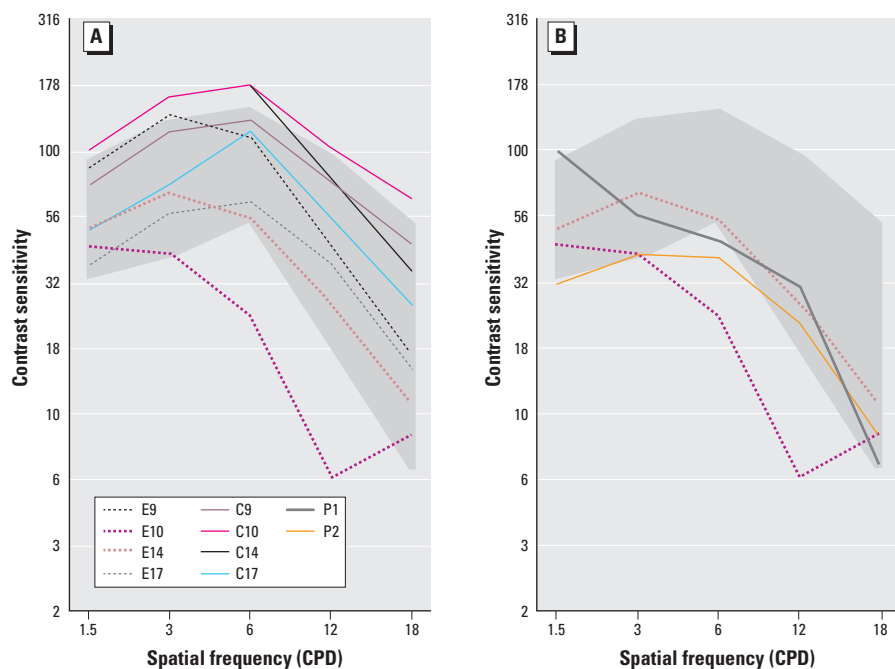
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## Update of Residential Tetrachloroethylene Exposure and Decreases in Visual Contrast Sensitivity

In "Apartment Residents' and Day Care Workers' Exposures to Tetrachloroethylene and Deficits in Visual Contrast Sensitivity," Schreiber et al. (2002) reported significantly lower visual contrast sensitivity (VCS) in apartment residents exposed to tetrachloroethylene (perchloroethylene, or perc) compared to unexposed "matched" control subjects. The authors stated that the VCS deficit may "represent a long-lasting, adverse alteration in neurobehavioral function" caused by chronic, environmental perc exposures, although they cautioned that methodologic limitations preclude definitive attribution of causation.

Residential data reported by Schreiber et al. (2002) were originally collected by the New York State Department of Health (NYSDOH) as a pilot project to support development of a larger study (NYSDOH, unpublished data). Residents exposed to perc included in the study were 13 adults from six households (20–72 years of age) and 4 children from three households (6–13 years of age) located in two buildings. Continued research by the NYSDOH and others (Farrar et al. 2001; NYSDOH 2004) suggests that confounding factors may influence VCS test performance of children in this and other studies. Consequently, we would like to update the findings of the residential study described by Schreiber et al. (2002).



**Figure 1.** Individual VCS functions of children. (A) VCS functions of perc-exposed child residents (E9, E10, E14, E17) and matched controls (C9, C10, C14, C17) included by Schreiber et al. (2002) and the NYSDOH (2000). (B) Individual VCS functions of children characterized as having DD or ADD included by Schreiber et al. (2002; E10, E14) and examined in the NYSDOH study (NYSDOH 2004; P1, P2). The gray band reflects the normal adult range (90% confidence limits) reported for the Functional Acuity Contrast Test, F.A.C.T 101 (Stereo Optical Co., Inc., Chicago IL).

In the analyses described by Schreiber et al. (2002), VCS of all perc-exposed adult and child residents and unexposed matched controls were compared using analysis of variance and SAS software (version 8.2; SAS Institute, Cary, NC). Matched pair, exposure (perc exposed, unexposed), and spatial frequency (cycles per degree) were independent variables; VCS was the dependent variable. The authors reported a significant effect of exposure on VCS ( $F = 19.38$ ;  $df = 1,144$ ;  $p < 0.001$ ). Sample sizes were not sufficient to support statistical analysis of VCS stratified by age (i.e., child, adult); VCS data were available for only four children. However, review of individual VCS functions suggested that the significant VCS deficit was likely to be attributable to the four children in the exposed group. VCS functions of the exposed children were therefore carefully examined with respect to VCS functions for their matched controls and with respect to information about the children available from parental questionnaires.

Individual VCS functions for each exposed child were lower than his/her matched control (Figure 1A). Although perc exposure may have influenced VCS of these children, other factors could have contributed to their poor performance. For example, conditions such as developmental delay (DD) and attention deficit disorder (ADD) are known to be associated with decreased VCS

(Farrar et al. 2001; Hudnell et al. 1996). One of the exposed children was characterized as having psychologist-diagnosed DD, and another exposed child was characterized as having physician-diagnosed ADD (Table 1). These two children performed poorly on the VCS but similar to unexposed children with similar diagnoses examined in a recently completed NYSDOH study (Figure 1B) (NYSDOH 2004). Also, another perc-exposed child was characterized as being forgetful at school, although not specifically as developmentally or learning disabled. (Questionnaires administered to residents of dry-cleaner buildings are part of NYSDOH records for the residential study; questionnaires were not completed for controls.) It is therefore possible that the perc exposure–VCS association reported by Schreiber et al. (2002) may have been confounded by the presence of these conditions.

In studies now being conducted by the NYSDOH and as reported by Scharre et al. (1990), 5- and 6-year-old children perform variably on the VCS test; sometimes they perform well, and sometimes they are inattentive and unable to perform. Two exposed children included in the residential study were 6 years of age. The matched control for one of these was 8 years of age, and the matched control for the other was the average of a 5-year-old and 7-year-old. Thus, although VCS was poor in perc-exposed child residents

**Table 1.** Child residents and matched controls in the VCS studies.

ID	Exposed		Matched control	
	Age	DD or ADD	ID	Age
Children <sup>a</sup>				
E9	8	–	C9	9
E10	6	X	C10	8
E14	12	X	C14	12
E17	6	–	C17	5.7
Children <sup>b</sup>				
P1	8	X		
P2	10	X		

<sup>a</sup>Children shown in Figure 1A (NYSDOH, unpublished data; Schreiber et al. 2002). <sup>b</sup>Children shown in Figure 1B; E10 and E14 from Schreiber et al. (2002) and P1 and P2 examined in the NYSDOH study (NYSDOH 2004).

compared to others not exposed to perc, this may have been partly due to differences between groups in factors other than perc exposure (e.g., age).

In an exploratory analysis, VCS was evaluated only among adult participants in the residential study. When VCS of perc-exposed adult residents and unexposed adult control subjects were analyzed alone, excluding the four child pairs, a significant effect of perc exposure was not observed ( $F = 2.04$ ;  $df = 1,108$ ;  $p = 0.16$ ). The sample size was small ( $n = 13$ ) and consequently the statistical power was limited; however, the results suggest that VCS was not significantly decreased in perc-exposed adult residents.

Clearly, the possible effect of perc on VCS in adults, and especially in children, should continue to be explored. However, as illustrated here and discussed by Swinker and Burke (2002) and Hudnell and Shoemaker (2002), the possible influence of factors other than perc exposure on VCS should also be considered. These factors include age and the presence of learning disabilities or developmental delay in children, as illustrated here, as well as conditions such as diabetes, high blood pressure, glaucoma, and cataracts, in adults (Bodis-Wollner and Camisa 1980).

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

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## Residential Tetrachloroethylene Exposure: Response

We are grateful for the opportunity to respond to Storm and Mazor's comments about our study "Apartment Residents' and Day Care Workers' Exposures to Tetrachloroethylene and Deficits in Visual Contrast Sensitivity" (Schreiber et al. 2002). We investigated potential relationships between environmental exposure to the dry-cleaning solvent perchloroethylene (perc, or tetrachloroethylene) and effects on visual function in two exposed populations (17 residents, including 4 children, in two apartment buildings and 9 adults working at a day care center) and age- and sex-matched control groups ( $n = 25$  and  $n = 9$ , respectively). Mean airborne perc concentrations were 778 and 2,150  $\mu\text{g}/\text{m}^3$  in the apartments and the day care center, respectively, levels well above the background range of  $< 1.6\text{--}22 \mu\text{g}/\text{m}^3$  [New York State Department of Health (NYSDOH) 1997]. Perc concentrations in biological samples were also elevated (Schreiber et al. 2002). We assessed visual function using tests of near acuity, near visual contrast sensitivity (VCS; a sensitive indicator of neurologic function), and color discrimination. Visual acuity did not differ between groups, but VCS scores from both the apartment residents and the day care workers were depressed across the spatial frequency spectrum, similar to results obtained in other solvent exposure studies (Broadwell et al. 1995; Campagna et al. 1995; Castillo et al. 2001; Donoghue et al. 1995; Frenette et al. 1991; Hudnell et al. 1996a; Mergler 1995; Mergler et al. 1991). We concluded that

Although the similar VCS deficits in both the residential study and day care investigation were apparently associated with chronic low-level environmental perc exposures, methodologic limitations preclude a definitive attribution of causation.

It is unlikely that age differences caused the group differences in VCS, as Storm and Mazor suggested. The exposed and control participants in the residential study were matched for age within 2 years, and the group means were within 1 year of each other. The mean age of the four exposed children was about 6 months greater than that of the six controls. The day care workers and controls were matched within 1 year of age, and the group means were within 6 months of each other. Such small age differences were highly unlikely to account for the VCS deficit.

Storm and Mazor reported that one exposed child was developmentally delayed and one had an attention deficit disorder, and they suggested that this may have caused the group difference in VCS. However, they did not provide comparable data for the control children, who were family members of NYSDOH employees. The same assessment of potentially confounding factors should have been applied to both groups. Furthermore, they cited a previously published article (Hudnell et al. 1996b) when suggesting that the VCS deficits in the exposed children may have been due to developmental delays. That article actually reported an association between perinatal exposure to airborne neurotoxins and developmental delay in VCS (Hudnell et al. 1996b). We felt that it was inappropriate to exclude children from study participation because of conditions that may have been caused by perc exposure.

As noted by Storm and Mazor, "sample sizes were not sufficient to support statistical analysis of VCS stratified by age (i.e., child, adult)" in the residential study. It is not surprising that when they reduced the sample size to 13 pairs by excluding all children, the  $p$ -value increased from  $< 0.001$  to 0.16, even though 7 of the 13 exposed adults had VCS scores in the lower 12th percentile of control scores.

We took several steps to minimize the influence of potentially confounding factors on VCS. A standard operating procedure and luminance control ensured test consistency. The exclusion criteria—failing to attentively complete the VCS test (one control resident excluded), having Snellen acuity worse than 20:70 (two eyes from exposed residents excluded, perhaps due to cataracts), and observing strabismus or other ocular anomalies (one control resident excluded)—were applied to both groups. None of the participants reported having an illness that might affect neurologic function. In the day care investigation, all participants were healthy females, and eight of nine were 21–29 years of age, thereby further reducing the potential for confounding. The

observation of similar reductions in the VCS spatial-frequency profiles of the residential and day care exposed cohorts supported our conclusion that the effects may have been due to perc exposure.

Storm and colleagues recently conducted a study of apartment residents potentially exposed to perc and reported normal VCS in the exposed cohort (NYSDOH 1999, 2003). However, two factors limited comparability to our study (Schreiber et al. 2002). First, they measured far, rather than near, VCS. Near and far VCS do not provide comparable data due to differences in illumination, near and far visual acuity, and the visual field size of the test stimuli. Second, the mean airborne perc concentration was 34  $\mu\text{g}/\text{m}^3$  in their study (NYSDOH 2003), 1–2 orders of magnitude lower than in our studies. These differences precluded an attempt to verify the VCS effects reported in our article (Schreiber et al. 2002). We stand by our methodologic procedures, results, and conclusions.

*This letter was reviewed by the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the agency.*

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

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## More Recent Studies on Fragrances

In response to Curtis (2004), I would like to cite more recent studies by researchers at the Research Institute for Fragrance Materials, Inc. (RIFM) that address the health and environmental effects of fragrances.

The RIFM strives to be the international leader for the safe use of fragrance ingredients (Balk et al. 2004; Bickers et al. 2003a; Cadby et al. 2002b; Smith 2003) and has ongoing research programs in the areas of fragrance allergy, human health effects (Cadby et al. 2002a; Bickers et al. 2003b), respiratory safety (Isola et al. 2004; Smith et al. 2004), and environmental impact (Salvito et al. 2002, 2004). The RIFM's comprehensive, logical, and documented research methods are modeled after the National Academy of Sciences' (NRC) Elements of Risk Assessment and Risk Management (NRC 1994).

Research is prioritized (Ford et al. 2000) and designed using information in the RIFM proprietary database (RIFM 2004) and according to the needs of the scientific community and the general public. The database provides a clearinghouse for human health and environmental studies, as well as basic material information, and is maintained by continuously monitoring journals, government reports, company-sponsored research, and available literature to enable analysis of documented conclusions.

All available information pertaining to the safety of fragrance materials, study protocols, and results are reviewed by an independent international panel of scientific and medical experts from the fields of toxicology, dermatology, pathology, and environmental science. Research results and safety evaluations are published in peer-reviewed scientific journals and presented at professional meetings.

In addition, the RIFM accepts proposals for sponsored scientific research and will work jointly with interested third parties to further knowledge on health and environmental issues.

*The author is employed by the Research Institute for Fragrance Materials; he declares that the RIFM publishes its work in the peer-reviewed literature under the guidance of an independent scientific panel and receives support from the private sector.*

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## Pesticides and Organic Agriculture

I read with horror the article “Pesticides and Parkinson Disease” by Renee Twombly (2004) in which she implied that rotenone is “often used in organic gardening and farming.” She went on to describe the effects of rotenone and the even more harmful effects of pyridaben, which is far more toxic than rotenone, both of which are used in conventional agriculture.

To set the record straight, rotenone is not commonly used in organic agriculture. Rotenone that has been naturally derived is listed as a “restricted substance” by the Organic Materials Review Institute (OMRI 2004) and may be used only in special circumstances with designated limitations. Meanwhile, rotenone's synergist, piperonyl butoxide, is prohibited from use in organic agriculture.

The premise of organic agriculture is to fortify the soil through wholesome, nontoxic means, thereby strengthening the ability of plants to defy diseases and pests.

It is the hope of the hardworking pioneers in the organic movement that the instance of Parkinson disease, cancer, and many environmentally related illnesses will diminish exponentially with the conversion of acreage to organic cultivation.

*The author declares she has no competing financial interests.*

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*Editor's response:* As DiMatteo implies, rotenone is, or should be, used only as a last resort in organic gardening and farming. It should be noted, however, that this pesticide is commonly marketed and sold under the rubric “organic gardening supplies.”

## Agricultural Task Not Predictive of Children's Exposure to OP Pesticides

Coronado et al. (2004) reported that the agricultural task of plant thinning by adults was associated with higher urinary pesticide metabolite concentrations in children. Their analysis was based on data from a 1999 study of farmworkers in the Yakima

Valley of Washington State (Curl et al. 2002; Thompson et al. 2003). Their conclusion was based on a finding that one of the three dimethyl dialkylphosphate (DAP) metabolites of the organophosphorus (OP) pesticides—dimethylthiophosphate (DMTP)—was more frequently detected among children living in the same household with adult farmworkers who reported having thinned plants compared with children living in the same household with farmworkers who did not report thinning (92% vs. 81%, respectively).

We examined the same data set to determine if the actual urinary pesticide metabolite concentrations, rather than simply the frequency of metabolite detection, differed between these groups of children. We used log-transformed data and the independent *t*-test (equal variance assumption) to determine differences between geometric mean metabolite concentrations. We found no significant differences between children of thinners versus non-thinners for any of the three DAP metabolites. Geometric mean values for DMTP were 6.13 µg/L for 136 children of thinners and 5.27 µg/L for 75 children of non-thinners ( $p = 0.41$ ). Furthermore, we did not find a significant difference between these groups for the sum of the dimethyl DAP metabolites (geometric means of 0.097 vs. 0.083 µmol/L;  $p = 0.33$ ).

Coronado et al. (2004) also suggested that children of thinners may receive higher exposures than children of pesticide handlers (mixers, loaders, applicators). We compared the children of thinners to children of handlers, excluding the 28 children for whom the corresponding adult farmworker reported both thinning and handling. No differences were observed between these groups for any of the three DAP metabolites. Geometric mean values for DMTP were 6.47 and 6.05 µg/L, respectively ( $p = 0.81$ ), and 0.10 and 0.096 µmol/L, respectively, for the sum of the dimethyl DAP metabolites ( $p = 0.78$ ). It is not surprising that the child population in this study exhibited high frequencies of detection of the DAP metabolites. The most recent study by the Centers for Disease Control and Prevention (Barr et al. 2004) found that 87% of U.S. children 6–11 years of age had one or more of the dimethyl DAP metabolites detected in their urine.

We conclude from our analysis of this data set that *a*) children living in households with thinners did not exhibit higher OP pesticide exposures than children living in households with workers in other agricultural task categories; and *b*) OP pesticide exposures did not differ between children of thinners and children of pesticide handlers. We further conclude that frequency of detection is an inadequate exposure metric

for urinary pesticide metabolites that are detected with high frequency, and that its use independent of metabolite concentration data can prove misleading. We recommend that future analyses of children's pesticide exposure focus on measured metabolite concentrations rather than the simple presence or absence of metabolites in biological samples.

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

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### Children's Exposure to OP Pesticides: Response to Fenske et al.

In our article (Coronado et al. 2004), we reported a higher proportion of urine samples containing detectable levels of the organophosphate (OP) pesticide urinary metabolite dimethylthiophosphate (DMTP) from children of farmworkers who reported having thinned plants, compared with urine samples from children of non-thinners. We reported the detection frequency for individual dimethyl metabolites, not a composite score for the detection of multiple dimethyl metabolites. We thank Fenske et al. for their additional analyses showing slightly higher, though not significant, concentrations of urinary DMTP in children of thinners versus non-thinners.

We knew that assessing detection frequencies would provide only a preliminary

view of a more complex pattern of exposure; thus, we specifically stated in the "Methods" section of our paper that the analysis was exploratory in nature. We examined job task as a factor possibly associated with high exposure to pesticides because job task is closely linked with regulatory policy. We understood that if substantial differences in the percentage of detectable samples existed between groups further exploration would be warranted.

This type of analysis follows the logic put forth by others in the field of exposure assessment. For example, Fenske et al. highlight that Barr et al. (2004)—in the same issue of *EHP* in which our article was published—provided detection frequencies of OP pesticide urinary metabolites in older children (6–11 years of age) from the general population. Barr et al. reported a detection frequency for DMTP of 69%, with a limit of detection of 0.18 µg/L. In our study we matched children (2–6 years of age) with an adult agricultural worker in the same home. Among the children matched to farmworkers who reported thinning, we observed a detection frequency for urinary DMTP of 92%, with a limit of detection of 1.1 µg/L.

We agree with Fenske et al. that a more in-depth analysis is warranted and thank them for their interest and recommendations.

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

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### Olden's Contributions

I read with mixed feelings of approval and sadness your editorial about the end of tenure for Kenneth Olden as director of the

National Institute of Environmental Health Sciences (NIEHS) (Brown et al. 2004). I have been greatly impressed with Olden's significant contributions to broadening the scope of public health sciences, as reflected in the evolution of *EHP* into an exemplary, innovative, and internationally highly respected journal on environmental health sciences.

Specifically, the following sentence in the editorial was grist for my mill:

From early on he showed awareness and understanding of a fact that had often been ignored by others in research administration—that local communities have the collective ability to identify environmental health problems but often lack the time, means, and research expertise to effectively resolve these problems.

We have just published a report describing a unique community–physician–scientist cooperative research effort without support from any public agency that has been—at least for a small number of survivors of this group of Hanford, Washington, “downwinders”—of great significance for their experiencing a sense of empowerment and, at least to some degree, of “justice” through the process of scientific validation (Nussbaum et al. 2004).

It seems that the efforts of our alliance might well have fallen within the boundaries of projects that Olden's initiatives could have supported: to provide and link communities with appropriate research resources.

I fear that Olden's departure will be a great loss for the NIEHS and that it will be very difficult to find a replacement for him with an equally bold vision and willingness to take risks in innovative leadership.

*The author declares he has no competing financial interests.*

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