Perfluorinated Compounds and Immunotoxicity in Children (Reply Letter)

Perfluorinated Compounds and Immunotoxicity in Children

To the Editor: Dr Grandjean and colleagues[1] suggested that perfluorinated compounds (PFCs) may increase a child's risk for not being protected against diphtheria and tetanus and may indicate the potential for other immune system deficits. Not cited were data that do not support their concern, and the authors did not adequately characterize immunotoxicology data.

A Danish study examined whether perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) may impair children's immune systems.[2] Fei et al[2] randomly selected 1400 pregnant women from 91 827 persons in the Danish National Birth Cohort between 1996 and 2002 and investigated their offspring's history of hospitalizations for infectious diseases through 2008 (n = 363 children). Prenatal serum concentrations of PFOS and PFOA, similar to the values in the study by Grandjean et al,[1] were not associated with hospitalizations for infectious diseases. Fei et al[2] concluded that their data did not support the hypothesis that prenatal PFOS and PFOA exposures decrease resistance to childhood infections.

Grandjean et al[1] did not provide a biological rationale for summing serum concentrations of PFCs in their analysis. Peters and Gonzalez[3] have cautioned against such a practice based on mechanistic arguments. Grandjean et al should have provided justification for summing PFOA, PFOS, and perfluorohexane sulfonic acid.

Grandjean et al stated that their "findings are supported by several, though not all, experimental studies in rodents, in which adverse effects of PFOS on humoral immune function were observed at serum concentrations similar to those reported in the present study and at levels prevalent in the United States." Geometric means were 27.3 ng/mL for mothers and 16.7 ng/mL for children. As support they cite a study by Peden-Adams et al[4] involving gastric lavage in B6C3F1 mice that found an immunological effect at a mean serum PFOS concentration of 92 ng/mL. Qazi et al,[5] however, found no immunological effects at a mean serum PFOS concentration of 11 600 ng/mL in a dietary study in the same strain of mice. We cannot find any other published study reporting an immunological effect near the serum concentration of PFOS cited by Peden-Adams et al.[4] Thus, the rodent immunotoxicology studies do not appear to support the inferences made by Grandjean et al.

We believe this information should be reassuring to those concerned with the immune system, childhood infectious diseases, and PFCs.

Larry R. Zobel, MD, MPH
Geary W. Olsen, DVM, PhD
John L. Butenhoff, PhD

Author Affiliation: Medical Department, 3M Company, St Paul, Minnesota (lzobel@mmm.com).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Zobel, Olsen, and Butenhoff are employees of and hold stock in 3M Company, a former manufacturer of PFOA, PFOS, and PFHxS.

1. Grandjean P, Andersen EW, Budtz-Jørgensen E, et al. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA*. 2012; 307(4):391-397.
2. Fei C, McLaughlin JK, Lipworth L, Olsen J. Prenatal exposure to PFOA and PFOS and risk of hospitalization for infectious diseases in early childhood. *Environ Res*. 2010;110(8):773-777.
3. Peters JM, Gonzalez FJ. Why toxic equivalency factors are not suitable for perfluoroalkyl chemicals. *Chem Res Toxicol*. 2011;24(10):1601-1609.
4. Peden-Adams MM, Keller JM, Eudaly JG, Berger J, Gilkeson GS, Keil DE. Suppression of humoral immunity in mice following exposure to perfluorooctane sulfonate. *Toxicol Sci*. 2008;104(1):144-154.
5. Qazi MR, Nelson BD, Depierre JW, Abedi-Valugerdi M. 28-Day dietary exposure of mice to a low total dose (7 mg/kg) of perfluorooctanesulfonate (PFOS) alters neither the cellular compositions of the thymus and spleen nor humoral immune responses: does the route of administration play a pivotal role in PFOS-induced immunotoxicity? *Toxicology*. 2010;267(1-3):132-139.

In Reply: Human exposures to PFCs, the subject of our article, are a result of both past and current production. In our study, we measured children's exposure prenatally and up to age 5 years and found an association between elevated exposure to PFOS and PFOA and reduced clinically protective antibody levels to diphtheria and tetanus at age 7 years. While diphtheria may not be a serious risk in many western communities, we offered an additional booster vaccination to the 43 children (9%) not adequately protected against diphtheria or tetanus at age 7 years. The underlying question about the effect of environmental chemicals on the competency of the immune system is more likely to be reflected by specific vaccine responses than by total hospitalization rates for infectious diseases.[1]

Regarding Dr Zobel and colleagues' concern about summing the PFCs as a supplement to standard regression analyses for each PFC compound, the factor analysis approach that we used allowed inclusion of the 3 major PFCs in a weighted exposure variable. In agreement with the regres-

sion analyses, the strengthened results provided adjustment for exposure imprecision and minimized concerns about multiple comparisons.

Experimental evidence supports the plausibility of our clinical findings. In support of laboratory models that revealed immunotoxicity at serum PFC concentrations similar to those documented in human populations,[2] PFCs also induce immunotoxic effects in human leukocytes in vitro at 100 ng/mL (the lowest concentration tested).[3]

The comments by Zobel et al illustrate the paradox that industrial chemicals in use for several decades are not subject to safety testing, while findings of adverse effects are often met with skepticism.[4] Our results suggest that a prudent public health response would aim at protecting children's immune systems against PFC exposures.

Philippe Grandjean, MD, DMSc
Carsten Heilmann, MD, DMSc

Author Affiliations: Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts (Dr Grandjean) (pgrand@hsph.harvard.edu); and Pediatric Clinic, Rigshospitalet-National University Hospital, Copenhagen, Denmark (Dr Heilmann).
Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Grandjean reported receiving a grant from the National Institute of Environmental Health Sciences and being employed by the National Board of Health in Denmark as a consultant on toxicology and environmental medicine. Dr Heilmann reported no disclosures.

1. van Loveren H, Germolec D, Koren HS, et al. Report of the Bilthoven Symposium: advancement of epidemiological studies in assessing the human health effects of immunotoxic agents in the environment and the workplace. *Biomarkers*. 1999;4(2):135-157.
2. Dewitt JC, Peden-Adams MM, Keller JM, Germolec DR. Immunotoxicity of perfluorinated compounds: recent developments. *Toxicol Pathol*. 2012;40(2):300-311.
3. Corsini E, Sangiovanni E, Avogadro A, et al. In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs). *Toxicol Appl Pharmacol*. 2012;258(2):248-255.
4. Sass J; Natural Resources Defense Council. The chemical industry delay game. http://www.nrdc.org/health/thedelaygame.asp. Accessed February 28, 2012.

Prognostic Models for Older Adults

To the Editor: Another factor to consider when evaluating prognostic indices for older adults[1] is whether their predictions for an individual agree. It is not well recognized, but different prognostic indices provide different estimates for the same individual and these differences can be substantial.[2,3] Based on this lack of reliability, Feinstein[4] suggested that clinicians instead rely on pertinent resemblance subgroups instead of multivariable methods. Thus, life expectancy estimates for patients of the same age, sex, and race from life tables may remain preferable, even when otherwise ideal prognostic indices are developed in the future.[5]

Ralph Stern, PhD, MD

Author Affiliation: Department of Internal Medicine, University of Michigan, Ann Arbor (stern@umich.edu).
Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported receiving retirement benefits and stock options from Pfizer.

1. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. *JAMA*. 2012;307(2):182-192.
2. Lemeshow S, Klar J, Teres D. Outcome prediction for individual intensive care patients: useful, misused, or abused? *Intensive Care Med*. 1995;21(9):770-776.
3. Stern RH. Individual risk. *J Clin Hypertens (Greenwich)*. 2012;14(4):261-264.
4. Feinstein AR. *Multivariable Analysis: An Introduction*. New Haven, CT: Yale University Press; 1996:566.
5. Gill TM. The central role of prognosis in clinical decision making. *JAMA*. 2012;307(2):199-200.

To the Editor: The study by Dr Yourman and colleagues[1] evaluated predictive models for survival in elderly adults as decision-making aids. Better life expectancy estimates may help avoid treatments in patients in whom high competing risks limit potential benefits. Several points merit consideration in this decisional context, beyond the usual metrics of model performance that are the focus of the review. First, predictions are not only point estimates but also, perhaps predominantly, probability distributions.

Second, cogent application of predictive models depends on an understanding not only of model accuracy (measured by the *c* statistic, bias, and other metrics) but also of the consequences of patient misclassification. To withhold or forgo potentially life-saving or beneficial treatment, patients and physicians often require a high degree of confidence that the conditions for futility are met. This requirement is unlikely to be met even from accurate and valid predictive models. For example, we recently reviewed 92 studies seeking to define groups of patients for whom treatment is futile and found that predictions are fundamentally unable to provide the degree of confidence that has been suggested as a standard for medical futility.[2,3]

Futility considerations might be raised when it is expected that a particular patient, on average, is not expected to survive past his or her "pay-off time" (the time to recoup the benefits of therapy). However, a wide probability distribution around this average risk means that treatment may be of benefit to some patients. Physicians who formally or intuitively recognize the limitations of risk estimation might therefore choose to offer tests and procedures even when accurate, validated predictive models indicate poor prognosis. For example, it has been observed that for terminally ill patients referred to hospice care, the mean ratio of predicted to observed survival was 5.3. This has been interpreted as reflecting inaccurate, overly optimistic prediction that results in late hospice referral.[4] However, such a result would also arise in a risk-averse decisional context in which there is an understandable tendency to minimize type I error, albeit at the expense of more type II error. Given the limitations of statistical prediction for the individual, the presence of accurate and valid prognostication for a patient population may not alter this trade-off; for some decisions, futile treatment in many may be the necessary price of success in a few.

Ezra Gabbay, MD, MS
David M Kent, MD, MS

Author Affiliations: Division of Adult Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel (Dr Gabbay) (gabbayez@hotmail.com); and Institute for Clinical Research and Health Policy, Tufts Medical Center, Boston, Massachusetts (Dr Kent).