Perfluorinated Compounds and Immunotoxicity in Children

To the Editor: Dr Grandjean and colleagues1 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 perfluoroctanoic acid (PFOA) may impair children’s immune systems.2 Fei et al2 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 al2 concluded that their data did not support the hypothesis that prenatal PFOS and PFOA exposures decrease resistance to childhood infections.

Grandjean et al3 did not provide a biological rationale for summing serum concentrations of PFCs in their analysis. Peters and Gonzalez4 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 involving gastric lavage in B6C3F1 mice that found an immunotoxic effect at a mean serum PFOS concentration of 92 ng/mL. Qazi et al5, 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.5 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).

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5. Qazi MR, Nelson BD, Dspielre 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 count? 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-

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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).

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Prognostic Models for Older Adults

To the Editor: Another factor to consider when evaluating prognostic indices for older adults1 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, Feinstein4 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.3

Ralph Stern, PhD, MD

Author Affiliation: Department of Internal Medicine, University of Michigan, Ann Arbor (stern@umich.edu).

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To the Editor: The study by Dr Yourman and colleagues1 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, Shear Zedek Medical Center, Jerusalem, Israel (Dr Gabbay) (gabbyez@hotmail.com); and Institute for Clinical Research and Health Policy, Tufts Medical Center, Boston, Massachusetts (Dr Kent).