Comments from Philippe Grandjean, MD (Harvard School of Public Health) and Esben Budtz-Jørgensen, PhD (University of Copenhagen)

In reference to the section on Imprecision (pp. 44-46) of the systematic review protocol and Appendix 2 (p. 23) we agree on the importance of exposure imprecision. However, the likelihood of differential error seems to be overemphasized. Especially in epidemiological studies of cohorts, measurement errors are generally non-differential. Under certain circumstances, measurement error may depend on the health outcome, as in case-control studies, where cases may remember any exposure more accurately or to a greater extent than the controls. However, if an exposure biomarker is used, the error is generally *non*-differential. As immunotoxicity of perfluorinated compounds (PFCs) is used by NTP in a pilot project, we offer the following example from our recent publication on the effects of PFCs on immune function in Faroese children (Grandjean et al, 2012). In this study, the exposure was measured at age 5, i.e., more than two years before the vaccine antibody outcomes at age 7.5 years. It seems highly unlikely that exposure error could be differential, i.e., biased in respect to the immune function two years later. Carroll (1998) makes the following general observation: "Nondifferential measurement error typically holds in cohort studies, but is often a suspect assumption in case-control studies". As is true for most cohort studies, whether retrospective, cross-sectional or prospective, the Faroese study cannot rule out an important degree of non-differential error. Thus, while the true causative PFC exposure may have occurred at some particular age or age range, our study utilized the serum-PFC concentrations at a single point of time, i.e., at age 5. Although PFCs have long elimination half-lives, the serum concentrations vary in time, thus causing (non-differential) imprecision of our exposure measurements and consequently an underestimation in our assessment of the immunotoxicity of PFC exposure. In other studies that we have carried out, e.g., on methylmercury neurotoxicity, we have documented that the relative error of an exposure biomarker (the maternal hair-mercury concentration) may be as large as 50% in terms of the coefficient of variation (Grandjean and Budtz-Jørgensen, 2010). Unfortunately, few epidemiological studies report the estimated or likely imprecision of the exposure assessment and do not include sensitivity analyses that attempt to adjust for the bias. For the NTP protocol, we find it of great importance that this issue is highlighted, and that imprecision-related bias toward the null is properly taken into account.

References

Carroll RJ. Measurement error in epidemiological studies. In: Encyclopedia of biostatistics (Armitage P, Coloton T, eds.). John Wiley & Sons, Chichester, 1998, pp. 2491-2519.

Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C. Decreased serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 2012; 307: 391-7.

Grandjean P, Budtz-Jørgensen E. An ignored risk factor in toxicology: The total imprecision of exposure assessment. Pure Appl Chem 2010; 82: 383-91.