Commentary: A step towards more comprehensive analyses of life course effects of mixtures of environmental factors

Miquel Porta,1,2,3* Magda Gasull1,2,3 and José Pumarega1,2,3

1Hospital del Mar Research Institute-IMIM, Barcelona, Spain, 2School of Medicine, Universitat Autònoma de Barcelona, Spain and 3CIBER en Epidemiología y Salud Pública (CIBERESP), Spain

*Corresponding author. Hospital del Mar IMIM UAB PRBB, Carrer del Dr. Aiguader 88, E-08003 Barcelona, Catalonia, Spain. E-mail: mporta@imim.es

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With its strengths and weaknesses, the analysis (‘association study’) of the relationships between environmental factors and lipid concentrations by Patel et al. is of great interest for at least five reasons.
First, few such analyses exist—so systematic and comprehensive—of the effects on physiological endpoints of common environmental contaminants and nutrients.\(^1\) Secondly, the study applied an innovative methodology; for a start, you may take a look at the figures (e.g. Figure 2, which does not only present actual empirical results, but may also draw a metaphor with a linkage disequilibrium plot or haplotype map).\(^1\) Thirdly, during the past 60 years, approximately, many human populations worldwide have experienced an unprecedented, generalized, chronic and systemic internal contamination by—not just ‘exposure’ to—mixtures of several thousand toxic substances.\(^3-6\) In industrialized countries, contamination in utero by some of such mixtures first became widespread for birth cohorts that are now approaching middle age, whereas cohorts with virtually no prenatal contamination are reaching old age and vanishing.\(^4\) Fourthly, many such pollutants are known to alter a range of physiological functions, and known or reasonably suspected to contribute to causing severe clinical effects and a substantial burden of disease.\(^7-16\) And fifthly, there is some evidence that a number of synthetic chemical agents may unfavourably alter lipid profiles; if true, the implications would be huge. (Of course, the time sequence is practically impossible to establish with cross-sectional studies alone, since many pollutants of concern are highly lipophilic.)\(^1\) Relatively, in the past few years over 90 studies indicated that some contaminants may contribute to cause components of the metabolic syndrome, including type 2 diabetes.\(^11,18\) A few of such studies were prospective and largely ruled out ‘reverse causality bias’.\(^1,11,18\) The effects of some mixtures (immunosuppressive, oxidative, inflammatory, neuroendocrine, non-genotoxic, epigenetic)\(^2,3,7-16\) may lie beneath—and partly explain—some intriguing disease–disease associations; e.g. between some cancers and obesity, diabetes, autoimmune or inflammatory disorders.\(^19\) In short, it is hard to explain on pure scientific grounds why the pollutants analysed by Patel et al.\(^1\) are not integrated more deeply into basic, clinical and epidemiological studies.\(^2,7-19\)

Indeed, ‘testing and reporting one or a few factors at a time can lead to a fragmented literature for environmental chemical factors’.\(^1\) However, although the implicit and explicit analogies that the paper makes between genome-wide association studies (GWAS) and environment-wide association studies (EWAS) are thoughtfully provocative, we cannot forget that the physico-chemical characteristics, functional properties and clinical effects of many environmental agents are better known than those of many genetic loci. Furthermore, analyses centred on individual pollutants may ‘miscalculate’ clinically or socially important adverse health effects, ‘potentially leading to lack of physiological coherence and public health relevance’.\(^1,7\) Fortunately, the study analysed a large number of contaminants and nutrients (some 188 agents and 13123 correlations between pairs of agents). Although such a number of factors has rarely been integrated in one single analysis, findings similar to those reported in the article\(^1\) have been published for the same and other compounds by previous studies. In this context, we concur that ‘by using transparent reporting and estimation of the false discovery rate’, the study partly overcomes the problem of selectively testing and reporting a few associations at a time.\(^5\)

The study did not aim at describing the most prevalent environmental mixtures, and did not analyse the (joint) effects on lipids of such combinations. Yet, as GWAS cannot assume that genes function independently, EWAS must cope with the fact that environmental exposures often interact. Neither GWAS nor EWAS can feign that genes and environmental exposures act individually (in the three facets of the expression).

Some estimates were adjusted for diabetes, blood pressure, waist circumference and body mass index, among other factors\(^1\)—a cautious approach. Yet, as also acknowledged by the authors, there may be over-adjustment, if some of the pollutants increase risk of obesity, diabetes or hypertension;\(^17\) and more even so if some pollutants indirectly alter lipid profiles. The excellent quantitative analyses\(^1\) reflect well current uncertainties on the relationships among lipids, environmental factors and chronic diseases.\(^11,17\)

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### How many chemicals do people accumulate during their lifetime?

All studies on human chemical contamination that measure concentrations in biological samples from individuals, focus on a limited set of compounds (due, mostly, to the need for large volumes of blood, urine or other media to analyse a large number of chemicals).\(^4\) Thus, it has so far been difficult to assess comprehensively to what mixtures is the general population significantly exposed in critical periods of life, how many persistent toxic pollutants do we accumulate during the life course or what is the number of chemicals whose presence in the body it is most relevant to analyse. Small series provide—anecdotal, but illustrative—evidence on these questions:

- In nine healthy volunteers from New York, a minimum of 77 chemical contaminants were found (out of 210 agents analysed) in the same individual; there were up to 106 compounds in one person.\(^6\)
- In a study comprising members of 13 families from 12 European countries, between 18 and 39 chemicals were found in any one individual (of 107 analysed); half of the subjects had 28 or more compounds detected.\(^20\)
In 155 volunteers from 13 locations in the UK, up to 49 chemicals were found in any one person (of 78 substances analysed); the median number was 27, and the minimum, 9.21

In a US nationally representative assessment of 268 pregnant women’s exposure to 163 chemicals,22 essentially all women were exposed to at least 43 chemicals. The median number of organochlorine pesticides detected was 6 (of 13 analysed). Across chemical classes, the median number ranged from 8 (of 17 analytes) to 50 (of 71 analytes). Polychlorinated biphenyls, organochlorine pesticides, phenols, polybrominated diphenylethers, phthalates and polycyclic aromatic hydrocarbons were detected in 99–100% of women.22

In a representative sample of the general population of Catalonia (n = 919), 8 pollutants (of 19 analysed) were detected (each) in >85% of subjects. No citizen was free from contaminants (nobody had less than three); and 73% of the population accumulated 10 or more chemicals.5,23

A few studies based on representative samples of the general population have assessed larger numbers of compounds: 212 in the US Fourth National Report on Human Exposure to Environmental Chemicals3 and 91 in Canada.24 Data on different chemicals in different sets of individuals who took part in different population-based studies could be pooled, integrated and modelled to estimate answers to the questions mentioned in the first paragraph of this section, including exposure estimates by age-cohort-period, and by gender, ethnic and socio-economic groups.4,5

The technical and economic barriers are as feasible to overcome as in other ‘high-throughput’ projects.

To conclude, the study by Patel et al.1 is an excellent reminder that (i) there are strong scientific reasons to integrate biomarkers of internal dose of environmental factors in basic, clinical and epidemiological research on the aetiopathogenesis of human diseases; (ii) many individuals accumulate mixtures of persistent toxic substances throughout the life course; (iii) knowledge on such exposures and their joint effects (including alterations of lipid profiles and metabolic functions) ought to be assessed more often when hypothesizing, analysing or interpreting causal scenarios; and (iv) it may be scientifically unfounded to study gene expression and the genetic bases of human diseases without considering environmental exposures and the hypothesis that, throughout the life course, key causal processes in the aetiopathogenesis of diseases of complex aetiology involve contamination by persistent toxic pollutants and the ensuing accumulation of genetic and epigenetic alterations.

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