scientific methods focus primarily on parts of a large system, not on the large system itself.

Another dimension of this change in focus is the development of "joining edge" research, in which leading ideas and best practices from multiple disciplines are brought together in a collaborative effort to examine large, complex systems. This approach complements the more familiar pursuit of progressively narrowing "cutting-edge" research of components of a whole system (Cairns 2003; Kriebel et al. 2001).

Perhaps, scientific data to advance human understanding about why global-scale human activities and systems are sustainable or unsustainable could be vital to protecting humanity from endangerment, biodiversity from extinction, and Earth from irreversible degradation, even in these early years of the 21st century.

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The Precautionary Principle: Schütz and Wiedemann Respond

Salmony rightfully points to various examples for potentially harmful effects of human activities that call for strategies to cope with ambiguous risks. The precautionary principle is seen by many as the answer to this problem. We agree that the precautionary principle formulates a sensible maxim for coping with uncertainty. However, we are less confident that it provides a feasible solution.

There are at least two problems with the application of the precautionary principle. The first, which we addressed in our article (Wiedemann and Schütz 2005), is that applying the precautionary principle might have unintended and unwelcome effects—in our case, increase public concern about radio frequency electromagnetic fields (RF EMFs). At least when precautionary measures are implemented to reassure the public, this runs counter to the original intention.

The second, perhaps more serious, problem of applying the precautionary principle is its "extreme variability in interpretation" (Foster et al. 2000). The decision to apply the precautionary principle depends on three factors: the type of evidence considered as appropriate for decision making, the amount of evidence, and the reference point for triggering the precautionary principle (how much evidence is enough?).

Roughly, three different types of evidence can be distinguished: scientific data, observations of health professionals, and personal experiences of lay people. The problematic issue is that some proponents of the precautionary principle consider scientific information, although necessary and important, not to be the exclusive basis for decision making. However, expanding the data basis beyond scientific information may result in conflicting claims about the significance of the various types of evidence. And there are no efficient procedures to resolve these conflicts.

The key question is whether there is enough scientific evidence to show that the risk potential might be real. Although ignorance and uncertainty exist, at least some evidence is required for triggering precautionary measures (World Health Organization 2000). That is, a hazard must be identified, and some understanding is needed about the conditions under which it is likely to occur. Therefore, a careful assessment of the available evidence is critical.

At present, there is no clear definition of the reference point for the decision to invoke precautionary measures. Without this clarification, any decision on applying the precautionary principle remains arbitrary.

Obviously, the answer to this question cannot be given by science alone (although science can provide important information). It will require value judgments, and it is ultimately a political decision. However, even if policy makers are bold enough to vote for precaution, the question remains about what to do.

Any well-founded decision about precautionary measures will also require some knowledge about the effectiveness of the precautionary measures that are to be taken. Unfortunately, in those situations for which the precautionary principle is intended, this knowledge is usually lacking.

The decision to implement precautionary measures needs to be justified by more than pointing at the possibility that a risk may exist. It needs evidence, and above all, a structured and transparent procedure for evaluating this evidence. For this, a solution is pending.

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Peripheral Arterial Disease and Metals in Urine and Blood

Navas-Acien et al. (2005) recently analyzed the data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES). They suggested that blood lead and blood and urinary cadmium, at levels well below safety standards, were associated with an increased prevalence of peripheral arterial disease (PAD) and that cadmium might partly mediate the detrimental arterial effects of smoking. The authors recognized that their findings needed confirmation and support from mechanistic studies. In line with their suggestion, we analyzed data from 428 participants in the Flemish Study on Environment, Genes, and Health Outcomes (Staessen et al. 1994). As described by Navas-Acien et al. (2005), we included only subjects who were at least 40 years of age and we defined PAD as an ankle brachial index of > 0.9 in at least one leg. Blood lead and blood and urinary cadmium were measured by atomic absorption spectrometry. The geometric mean concentrations were

0.43 nmol/L [5th–95th percentile interval (PI), 0.19–1.03] for blood lead and 11.6 nmol/L (PI, 3.6–31.1) for blood cadmium. The urinary cadmium excretion averaged 11.6 nmol/24 hr (PI, 3.8–35.5).

We adjusted for demographic and cardiovascular risk factors. For blood lead and cadmium, the odds ratios of PAD comparing quartiles 2–4 with the lowest quartile were in line with those of Navas-Acien et al. (2005). However, for the 24-hr urinary cadmium excretion the *p*-value for trend was only 0.72. Urinary cadmium is a more precise biomarker of exposure than blood cadmium, because urinary cadmium reflects lifetime exposure and blood cadmium reflects more recent exposure. Navas-Acien et al. (2005) measured only metal concentrations in spot urine samples (Navas-Acien et al. 2005), whereas we measured the 24-hr excretion of cadmium. We could not demonstrate any relation between cardiovascular disease or the incidence of hypertension in relation to environmental exposure to lead and cadmium (Staessen et al. 2000). We therefore concur with their conclusion that the role of cadmium in the pathogenesis of atherosclerosis needs further research. However, not only are mechanistic studies required but also population studies, for example, that relate pulse wave velocity to biomarkers of cadmium exposure. We currently have similar experiments in progress.

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Peripheral Arterial Disease and Metals: Navas-Acien et al. Respond

We thank Plusquin et al. for their interest in our analysis of the 1999–2000 National Health and Nutrition Examination Survey (NHANES) data on the association of lead, cadmium, and other metals with the prevalence of peripheral arterial disease (PAD) (Navas-Acien et al. 2004; Navas-Acien et al. 2005). After analyzing data from 428 participants in the Flemish Study on Environment, Genes, and Health Outcomes, Plusquin et al. confirmed our findings of a positive and strong association between blood lead or cadmium with PAD. They also reported a nonstatistically significant trend for the association of 24-hr urinary cadmium with the prevalence of PAD; however, in the absence of information on relevant methodologic details, such as the number of subjects with PAD, this nonsignificant result is difficult to interpret. Overall, the findings of Plusquin et al. add to the growing concern about the cardiovascular effects of environmental exposure to low concentrations of metals (Weinhold 2004).

On a more general note, both the NHANES study, which was the basis of our analyses, and the Flemish Study on Environment, Genes, and Health Outcomes (Plusquin et al.) used cross-sectional designs. These designs have important limitations for assessing the causal effects of exposures on cardiovascular risk, even when the outcome is a subclinical marker such as PAD defined using the ankle-braquial blood pressure index. Some limitations of cross-sectional designs include survivor effects for severe cases of cardiovascular disease, potential changes in biomarker levels associated with disease development or with cardiovascular medications, and changes in exposure patterns associated with the development of disease. Although cross-sectional studies are important first steps in evaluating the cardiovascular effects of environmental exposures, prospective studies ultimately will provide more rigorous tests of causality. For cadmium, there are no prospective studies using biomarkers of exposure and adequate measures of cardiovascular disease incidence and mortality, whereas for lead the prospective evidence is limited (Lustberg and Silbergeld 2002; Moller and Kristensen 1992; Pocock et al. 1988). Because of the frequent environmental exposure to lead, cadmium, and other metals; the existence of a biological basis for cardiovascular effects of metals; and the current controversies on safety standards, performing high quality prospective studies with appropriate biomarkers of exposure and standardized cardiovascular outcome definitions is a public health research priority.

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Erratum

The publication date for an article cited by Do et al. [Chlorination Disinfection By-products and Pancreatic Cancer Risk. Environ Health Perspect 113:418–424 (2005)] was incorrectly given as 2004. The correct reference is as follows:

Wilkins JR III, Comstock GW. 1981. Source of drinking water at home and site-specific cancer incidence in Washington County, Maryland. Am J Epidemiol 114:178–190.