The European “Year of the Air”: fact, fake or vision?

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The European Commission (EC) has announced 2013 the “Year of the Air” declaring that air pollution remains a concern for public health and the environment despite obvious progress in the reduction of emissions of different air pollutants over the last decades. To improve the situation, the EC is currently reviewing their strategy on air pollution and related policies, also supported, for example, by results from a public survey based on 25,000 responses out of 506 million citizens in Europe (European Commission 2013).

Specific action seems to be necessary, because current EU standards for ambient air quality are weaker than those recommended by the World Health Organization (WHO) who intends to minimize health effects of air pollutants worldwide.

EU affiliated organizations such as European Environment Agency (EEA), European Environmental Bureau

(EEB) or the EC Joint Research Centre (JRC) as well as international organizations like WHO or Health Effects Institute (HEI) provide extensive pooled information on air pollution-related health effects, partially looking at certain air pollutants or specific situations and their impact. Nevertheless, speakers at the current HEI’s Annual meeting in San Francisco summarized and concluded that many components of the particulate matter mixture appear to be associated with some effects, but no specific component has been associated with all effects (EEA 2013; European Commission 2013; HEI 2010a, b, 2013; IIASA 2013; WHO Regional Office for Europe 2013a, b).

The WHO Regional Office for Europe is implementing two projects: (a) evidence on health aspects of air pollution, to review EU policies—REVIHAAP; and (b) health risks of air pollution in Europe—HRAPIE; with financial support from the European Commission (EC). (WHO Regional Office for Europe 2013a). Furthermore, Thematic Strategy on Air Pollution (TSAP) was started (IIASA 2013): “The European Commission is currently reviewing the EU air policy and in particular the 2005 Thematic Strategy on Air Pollution. It is envisaged that in 2013 the Commission will present proposals for revisions of the Thematic Strategy.” Following REVIHAAP’s (WHO Regional Office for Europe 2013a) decision, the HRAPIE project (WHO Regional Office for Europe 2013b) concluded for TSAP (IIASA 2013): “The core cost-effectiveness analysis is to include estimates of impact of long term (annual average) exposure to PM_{2.5} on all-cause (natural) mortality in adult populations (age 30+), based on a linear CRF (cumulative risk function), with relative risk of 1.062 (95 % CI 1.040–1.083) per 10 µg/m³. The impacts are to be calculated at all levels of PM_{2.5}.” These mortality coefficient estimates for the CRF were taken from the meta-analysis of Hoek et al. (2013).

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Poor air quality is estimated to cause nearly half a million premature deaths in Europe each year and is supposed to be associated not only with health effects, but also with high economic costs such as hospital admissions, lost working days and damage to ecosystems. Assuming that these statements are well supported, it is surprising how little basic data are available today: Information comparing current air quality levels with air pollution levels of some decades ago is very limited as well as longitudinal information about the individual behavior like indoor versus outdoor exposure or smoking habits although these variables may have large impact on the observed health effect estimates. Not really surprising is the fact that it is still unclear which substance(s) dominates health effects, due to the unspecific term “air pollution” or “bad air quality,” nor are devices and strategies well described how to perform accurate measurements of air pollutant substances (HEI 2010a, b).

Additionally, European actions regarding the “Year of the Air” are being seconded by activities of the International Agency for Research on Cancer (IARC) in Lyon, which has announced a workshop on October 2013 to discuss relationships between ambient air pollution and cancer, aiming at classifying “air pollution” (or certain components?) as carcinogenic substance(s). (IARC Workshop109, see <http://monographs.iarc.fr/ENG/Meetings/index.php>). Stimulated by these events, we are going to present and discuss some of the epidemiological studies that we believe are the most influential ones.

The discussions at this important IARC monograph workshop 109 are expected to focus on lung cancer risk in adults after long-term exposure to environmental pollutants although the evaluations will probably not be restricted to this topic (Ghosh et al. 2013). One study that will inevitably be discussed at that working group meeting in Lyon is the investigation of “air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from ESCAPE, the European Study of Cohorts for Air Pollution” (Raaschou-Nielsen et al. 2013). The authors reported a statistically significant association between risk for lung cancer and PM_{10} [meta-hazard ratio 1.22 (95 % CI 1.03–1.45) per $10 \mu\text{g}/\text{m}^3$]. For $\text{PM}_{2.5}$, the meta-hazard ratio was 1.18 (0.96–1.46) per $5 \mu\text{g}/\text{m}^3$. Interestingly, Raaschou-Nielsen et al. (2013) found no proof of heterogeneity across the studies: $I^2 = 0.0$, $p_{\text{het}} = 0.92$. We reanalyzed the data given in Fig. 3 by splitting the group into a Northern and Southern sub-study as indicated in Fig. 1. We obtained the following meta-hazard ratios for the countries north of the Alps (Sweden, Norway, Denmark, The Netherlands, UK; nine studies): 1.06 (95 % CI 0.80–1.39, $p = 0.69$) per $10 \mu\text{g}/\text{m}^3 \text{PM}_{10}$ and 0.92 (95 % CI 0.63–1.33, $p = 0.65$) per $5 \mu\text{g}/\text{m}^3 \text{PM}_{2.5}$. This indicates no overall effect based on the northern cohorts. An analysis of the complementary

data from Austria, Italy, and Greece (five studies) showed significant excess risks: The meta-hazard ratios were 1.34 (95 % CI 1.08–1.65, $p = 0.008$) per $10 \mu\text{g}/\text{m}^3 \text{PM}_{10}$ and 1.33 (95 % CI 1.03–1.71, $p = 0.028$) per $5 \mu\text{g}/\text{m}^3 \text{PM}_{2.5}$. A meta-regression estimated the relative risks (north vs. south) as 0.79, $p = 0.21$, for PM_{10} and 0.69, $p = 0.13$, for $\text{PM}_{2.5}$. Inconsistencies are difficult to identify as statistically significant because tests of heterogeneity are usually insensitive (Higgins et al. 2003; Rothman et al. 2008). Thus, the observed difference between the two geographical regions should instigate a search for reasons for this discrepancy although heterogeneity p values did not fall below the usual significance level of 5 %. Note that the low overall I^2 and the high overall p_{het} were misread by the authors and the Editors of Lancet Oncology as definite proof of homogeneity (this misunderstanding had the Editors reject our submitted Letter to the Editor).

Let us have a look from the same perspective at the influential meta-analysis by Hoek et al. (2013) that is used by HRAPIE (WHO Regional Office for Europe 2013b) and TSAP (IIASA 2013) to revise the EU air policy. The authors wrote about their finding on overall mortality: “A formal test of heterogeneity was statistically significant,” with an I^2 value of 65 % indicating moderate heterogeneity. When discussing Raaschou-Nielsen et al. (2013), we already have seen before that even a low overall I^2 and a large overall p_{het} cannot rule out relevant discrepancies between subgroups of studies. A significant $p_{\text{het}} < 0.05$ as reported by Hoek et al. (2013) proves heterogeneity between studies. And it appears to be euphemistic to qualify this and the $I^2 = 65$ % as “moderate.” In conclusion, Hoek et al. (2013) and the economic evaluations of the EU based on it by TSAP (IIASA 2013) suffer from significant heterogeneity. Thus, it appears to be problematic to apply this risk estimate from Hoek et al. (2013) in secondary calculations as if it were valid throughout Europe and invariant across time.

Heterogeneity may point to residual confounding and effect modification between and within studies as we will discuss in the following.

Another study that may be of relevance at the IARC meeting in October reported on lung cancer incidence in relation to long-term exposure to three ambient air pollutants and proximity to major roads, using a Canadian population-based case–control study (Hystad et al. 2013). The estimated increase in lung cancer incidence (expressed as an odds ratio) was 1.29 (95 % CI 0.95–1.76) with a ten unit increase in $\text{PM}_{2.5}$ ($\mu\text{g}/\text{m}^3$). This study struggles with confounding, in particular from smoking. Table 1 demonstrates the pronounced impact of smoking and socioeconomic status on lung cancer incidence within the study. Table 3 shows that the estimated effect of $\text{PM}_{2.5}$ depends considerably on the kind of adjustment chosen by Hystad et al.

(2013). Interestingly, Table 4 shows effect estimates among never smokers. Although of low precision (only 1,381 never smokers could be studied, among them 120 lung cancer cases), Table 4 in Hystad et al. (2013) reported an unexceptional odds ratio of 0.95 for $\text{PM}_{2.5}$ (per 10 $\mu\text{g}/\text{m}^3$ increase). Similar observations were made in a large pooled case–control study (Olsson et al. 2011) on workers exposed to diesel motor emissions (DME). This study could report on the effect of DME exposure on lung cancer incidence in 5,574 never smokers (among them 801 cases). Table 3 (Olsson et al. 2011) shows increases in lung cancer risk due to DME exposure in the full study group after adjustment for smoking, but no effect of exposure if the analysis is restricted to never smokers. Thus, residual confounding by smoking is an important topic.

Examples show that smoking as a potential cause of mortality is too often dismissed. The German East–West mortality difference narrowed rapidly after the 1990 unification, particularly for women. Many reasons were suggested (see Myrskylä and Scholz 2013). However, the authors showed that the role of smoking was underestimated and they presented convincing arguments that the reversing East–West mortality difference among German women could be explained by different trends in smoking habits between women in the East and West.

Thus, studies on never smokers are important. One impressive study is available (Turner et al. 2011) that investigated the effect of long-term ambient particulate exposure on lung cancer in 188,699 lifelong never-smokers drawn from the nearly 1.2 million participants of the Cancer Prevention Study-II, enrolled by the American Cancer Society in 1982 and followed prospectively through 2008. The authors found that each 10 mg/m^3 increase in $\text{PM}_{2.5}$ concentrations was associated with a 15–27 % increase in lung cancer mortality. However, the detected impact of covariates on dust effects is confusing: e.g., body mass index was strongly negatively correlated with the particle effect. The $\text{PM}_{2.5}$ effect was not seen in obese people who had a body mass index $>25 \text{ kg}/\text{m}^2$ at the start of follow-up. Why does this study find an effect of dust exposure in people with normal weight only? We cannot imagine a plausible causal mechanism that helps explain this observation. Thus, this large study on never smokers may suffer from uncontrolled biases.

Why are we so critical about these large studies? Everything appears to be obvious if we look at the risk estimates produced. Why should we care so much about heterogeneity, confounding and effect modification?

The main reason is that the expected effect estimate is very small. Thus, we need large studies to achieve the necessary precision. But large studies do not guarantee that the risk estimate is reliable. A new problem emerges that small studies do not suffer from: Bias considerations become a

paramount importance because the variances of the estimators do no longer cover potential biases (Hense 2011; Morfeld and Erren 2011). Detailed bias adjustment procedures may change interpretations, in particular in studies where the precision is high and results appeared to be obvious at first glance (Morfeld and McCunney 2010). Furthermore, the exposure assessment in the long-term ambient particle studies is neither very sensitive nor specific—almost never done longitudinally and almost always based on ecological data only. This opens the door for biases to distort the estimates of particle effects. Basagaña et al. (2013) investigated land-use regression models (LUR) that are often used to estimate exposures in environmental epidemiology studies and reported: “we show that in realistic cases where LUR models are applied to health data, bias in health effect estimates can be substantial. This bias depends on the number of air pollution measurement sites, the number of available predictors for model selection, and the amount of explainable variability in the true exposure.”

Candidate variables that may have distorted the findings of environmental studies are abundant. Occupational exposures are rarely controlled for although their impact has been described as substantial (Rushton et al. 2012) and different job histories are expected in different areas (rural vs. urban, rich vs. poor, etc.). Estimates of indoor exposures are difficult to incorporate (Dons et al. 2011). Other important variables may be associated with the living areas. Jokela et al. (2013) demonstrated the role of personality phenotype on mortality—see also the commentary by Chapman (2013). Mackenbach and Looman (2013) showed again the strong link between life expectancy and economic indicators.

Another reason to be cautious stems from mechanistic considerations. Exposures to poorly soluble particles are described to have a threshold effect on health, e.g. Pauluhn (2011). Objective procedures to search for thresholds in environmental studies are available but not applied (Morfeld et al. (2013).

Thus, it appears to be of major importance that the working group at the IARC monograph meeting 109 and other relevant bodies do much more than producing big books that list risk estimates and describe the many studies. The work actually needed is a critical appraisal of the available investigations. A strong branch in philosophy argued that the essence of true science is to search for weaknesses and even to strive for falsification (Popper 1935). Unfortunately, the composition of the upcoming working group meeting at IARC does not allow us to expect that such a critical appraisal will be performed. Some of the principal investigators who published the influential papers discussed above are invited as experts to evaluate their own work (see <http://monographs.iarc.fr/ENG/Meetings/vol109-participants.pdf>). This is not a novel observation, but a weakness the IARC monograph program suffers from for a

longer time. Erren (2011) asked: “how likely is the expectation that these ‘experts’ will review and challenge their own research appropriately?” McLaughlin et al. (2010) commented on this conflict of interest: “The claim by Coglianor and Straif that use by IARC of an interdisciplinary working group somehow precludes overinterpretation of epidemiological results is overly simplistic. Investigators selected for a working group, regardless of discipline, often have a vested interest in the decision process because of their own research results related to the deliberations. The routine inclusion as working group members of such self-interested investigators, as well as other persons identified with, and often professionally committed to, the exposure—cancer association under examination, is the quintessential conflict of interest.” Similar problems were reported in other fields of medicine (Bonneux and Van Damme 2010).

We hope that the critical voices of observers are listened to at the upcoming IARC working group meeting 109. But we cannot expect a critical evaluation of the studies by the very authors who have performed these investigations (Gamble 2012). For the sake of science as described by Popper and others, we hope that the critical perspective will become the main perspective when appraising studies so that the European “Year of the Air” will become a year that is not dominated by fake and poor predictions, but by facts.

Conflict of interest The authors declare that they are members of the research committee and scientific advisory group of the European Research Group on Environment and Health in the Transport Sector (EUGT, www.eugt.org).

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