



CORRESPONDENCE

Penh is not a measure of airway resistance!

To the Editors:

We wish to express serious concern about an article in the current issue of the *European Respiratory Journal*, in which MEHTA *et al.* [1] reported the effects of choline treatment on airway hyperresponsiveness using unrestrained plethysmography to derive enhanced pause (Penh) as a measure of lung function. In the Methods section of their paper, MEHTA *et al.* [1] refer to a previous study by LUNDBLAD *et al.* [2] in support of their statement: “Lung function was recorded and calculated as enhanced pause (Penh), which correlates with pulmonary resistance [2].” In fact, LUNDBLAD *et al.* [2] argued precisely the opposite, emphasising that unrestrained plethysmography accurately reflects airway resistance only if the gas in the plethysmograph is pre-conditioned to body temperature and humidity, and if functional residual capacity and tidal volume are measured independently. Indeed, it has been shown that Penh may not correlate at all with lung mechanical function [3, 4], and a distinguished group of experts has pointed out that it is scientifically unacceptable to report Penh as a measure of respiratory mechanical function [5].

The mechanical properties of the lungs are characterised by its main determinants, resistance and elastance. The resistance is the ratio of the pressure to the flow, while the elastance is the ratio of the pressure to the volume. Therefore, to calculate either of these quantities two signals need to be measured, namely pressure and either flow or volume. Penh is based on only a single time-varying signal, the pressure inside a plethysmograph, so it simply does not contain the information required to provide a valid estimate of lung mechanics. At best, Penh represents some kind of nonspecific reflection of the pattern of breathing [3]. MEHTA *et al.* [1] report that intranasal administration of choline was more effective than oral administration in reducing Penh. What this means in terms of the effects of choline on lung mechanics is anyone's guess, and could mean nothing at all. Moreover, because mice are obligatory nose breathers, Penh includes the mechanical properties of the nose which may be altered by intranasal

delivery. Penh has been thoroughly discredited as a measure of respiratory mechanics, and reviewers, editors and journals should not accept any study that uses this quantity and claims it represents airway or pulmonary resistance.

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STATEMENT OF INTEREST

None declared.

REFERENCES

- 1 Mehta AK, Gaur SN, Arora N, Singh BP. Effect of choline chloride in allergen-induced mouse model of airway inflammation. *Eur Respir J* 2007; 30: 662–671.
- 2 Lundblad LKA, Irvin CG, Adler A, Bates JHT. A reevaluation of the validity of unrestrained plethysmography in mice *J Appl Physiol* 2002; 93: 1198–1207.
- 3 Adler A, Cieslewicz G, Irvin CG. Unrestrained plethysmography is an unreliable measure of airway responsiveness in BALB/c and C57BL/6 mice *J Appl Physiol* 2004; 97: 286–292.
- 4 Petak F, Habre W, Donati YR, Hantos Z, Barazzzone-Argiroffo C. Hyperoxia-induced changes in mouse lung mechanics: forced oscillations *versus* barometric plethysmography *J Appl Physiol* 2001; 90: 2221–2230.
- 5 Bates JHT, Irvin CG, Brusasco V, *et al.* The use and misuse of Penh in animal models of lung disease *Am J Respir Cell Mol Biol* 2004; 31: 373–374.

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Particulate matter, science and European Union policy

To the Editors:

The editorial of ANNESI-MAESANO *et al.* [1] summarises current evidence concerning the adverse health effects of particulate matter (PM) and correctly outlines that: 1) the health effects of air pollution are a big problem worldwide; and 2) several scientific questions are still open. In addition, the authors press for more stringent measures of prevention, in order to achieve adequate protection of the exposed population. In particular,

they outline that “experimental research has rapidly progressed” and only “details of the pathophysiological mechanisms remain to be elucidated”.

We agree with most of their statements and are in favour of more stringent rules for the European Union (EU). However, we would like to make some comments concerning the open questions, in order to increase the scientific strength that should convince EU authorities.

The World Health Organization estimates that inhalation of PM in ambient air causes 500,000 premature deaths·yr⁻¹ [2]. A study from Los Angeles (CA, USA) reported a 17% mortality rise for an increase of 10 µg·m⁻³ in the concentration of particles with a 50% cut-off aerodynamic diameter of 2.5 µm [3]. These studies and reports may support the argument that PM kills a significant proportion of single individuals, and many politicians or officers compare these premature deaths to those due to work or traffic accidents. But what is the exact significance of PM that kills people? And what does premature death due to PM mean? There is an enormous gap, a huge grey area, between attributed deaths from epidemiological studies and the sum of single individuals who die because of PM.

Each disease has its own pathophysiological mechanism, according to which the various factors cause their effects or determine their health damage, derived from the toxicity or genotoxicity of the inhaled PM, but also from individual susceptibility, host response and the cumulative risk of the subject (for chronic obstructive pulmonary disease, coronary disease, diabetes *etc.*).

It would be desirable that epidemiological studies, the evidence of which will invariably be very weak in a complex condition such as PM-related disease, were paralleled by and coupled with more robust evidence concerning the exact role of each pollutant, the impact of the individual susceptibility of the host, previous chronic diseases of each subject and the pathophysiological mechanisms of host-pollutant interactions in individuals, leading to a wide variety of well-defined diseases.

Currently, there exist, on the one hand, epidemiological and toxicological studies and, on the other, data and reports from the clinical world. However, there is a third area between these other two that must be explored. It is necessary to bridge the gap between the microcytological and subcellular world (stress oxidation, cytokine production *etc.*) and macrobiology, organ failure, parenchymal dysfunction and shock, which involve the entire organism.

Pollutants interfere with a range of mechanisms relevant to the observed diseases, concerning both long-term exposure and short-term effects [4, 5], including sudden cardiac deaths and myocardial infarction, which could be triggered by particulate air pollution in susceptible people.

The aforementioned details include the role of old age, diabetes and chronic respiratory infections in frail patients predisposed towards the occurrence of myocardial infarction or cardiac arrhythmia, which could be treated or prevented by, for instance, antibiotics or a diet richer in omega-3 fatty acids. These details also include pathological findings, which might

only be available on biopsy [6] or necropsy in single subjects who died due to PM.

The questions that remain open include the following. 1) What are the pathophysiological mechanisms responsible for the health effects of PM? 2) Who are the subjects at greater risk? 3) On the basis of which tests can they be detected? 4) What efficient and cost-effective measures could help in prevention or treatment? 5) How can generic morbidity and mortality from epidemiological studies be correlated with health damage, *i.e.* well-characterised diseases, in single individuals?

In conclusion, we agree that the proposed European Union directive does not adequately reflect the best scientific evidence. However, there remains a duty to attempt to reduce the degree of uncertainty and provide more robust evidence from the available data, in particular concerning details of cause and effect relationships and pathophysiological mechanisms, facilitating the prevention and cure of single individuals. Last but not the least, a clear-cut answer to these details would strengthen the claims of scientists for more drastic and effective preventative measures by governments and those responsible in the European Union.

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STATEMENT OF INTEREST

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REFERENCES

- 1 Annesi-Maesano I, Forastiere F, Kunzli N. Particulate matter, science and EU policy *Eur Respir J* 2007; 29: 428–431.
- 2 Rom WN, Samet JM. Small particles with big effects *Am J Respir Crit Care Med* 2006; 173: 365–366.
- 3 Jerrett M, Burnett RT, Pope CA 3rd. Spatial analysis of air pollution and mortality in Los Angeles *Epidemiology* 2005; 16: 727–736.
- 4 Gualtieri M, Rigamonti L, Camatini M. Toxicity of tire debris extracts on human lung cell line A549 *Toxicol In Vitro* 2005; 19: 1001–1008.
- 5 Mantecca P, Gualtieri M, Camatini M. Tire debris organic extract affects *Xenopus* development *Environ Int* 2007; 33: 642–648.
- 6 Ghio AJ, Gilbey JG, Roggli VL. Diffuse alveolar damage after exposure to an oil fly ash *Am J Respir Crit Care Med* 2001; 164: 1514–1518.

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