Environ. Sci. Technol. **2010,** *44,* 476–482

Concentration Response Functions for Ultrafine Particles and All-Cause Mortality and Hospital Admissions: Results of a European Expert Panel Elicitation

GERARD HOEK,*,† HANNA BOOGAARD,† ANNE KNOL,‡ JEROEN DE HARTOG,†,‡ PAULINE SLOTTJE,†,‡ JON G. AYRES,§ PAUL BORM,|| BERT BRUNEKREEF,†,⊥ KEN DONALDSON,# FRANCESCO FORASTIERE,▽ STEPHEN HOLGATE,○ WOLFGANG G. KREYLING,◆ BENOIT NEMERY,¶ JUHA PEKKANEN,+,@ VICKI STONE,$ H.-ERICH WICHMANN,%,& AND JEROEN VAN DER SLUIJS=

Institute for Risk Assessment Sciences and Copernicus Institute, University of Utrecht, Utrecht, The Netherlands, Dutch National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands, Institute of Occupational & Environmental Medicine, University of Birmingham, Birmingham, U.K., Centre of Expertise in Life Sciences, Hogeschool Zuyd, Heerlen, The Netherlands, Julius Center For Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands, University of Edinburgh Centre for Inflammation Research, Edinburgh, U.K., Department of Epidemiology, Health Authority Rome, Rome, Italy, School of Medicine, University of Southampton, Southampton, U.K., Institute of Inhalation Biology and Institute of Epidemiology, Helmholtz Center Munich, Neuherberg, Germany, Lung Toxicology Research Unit, K. U. Leuven, Leuven, Belgium, Unit of Environmental Epidemiology, National Public Health Institute, Kuopio, Finland, School of Public Health and Clinical Nutrition, University of Kuopio, Finland, School of Life Sciences, Napier University, Edinburgh, U.K., and IBE-Chair of Epidemiology, Ludwig Maximilians University, Munich, Germany

Received July 17, 2009. Revised manuscript received October 28, 2009. Accepted November 5, 2009.

Toxicological studies have provided evidence of the toxicity of ultrafine particles (UFP), but epidemiological evidence for health effects of ultrafines is limited. No quantitative summary currently exists of concentration−response functions for ultrafine particles that can be used in health impact assessment. The goal was to specify concentration−response functions for ultrafine particles in urban air including their uncertainty through an expert panel elicitation. Eleven European experts from the disciplines of epidemiology, toxicology, and clinical medicine selected using a systematic peer-nomination procedure participated. Using individual ratings supplemented with group discussion, probability distributions of effect estimates were obtained for all-cause mortality and cardiovascular and respiratory hospital admissions. Experts judged the small database of epidemiological studies supplemented with experimental studies sufficient to quantify effects of UFP on all-cause mortality and to a lesser extent hospital admissions. Substantial differences in the estimated UFP health effect and its uncertainty were found between experts. The lack of studies on long-term exposure to UFP was rated as the most important source of uncertainty. Effects on hospital admissions were considered more uncertain. This expert elicitation provides the first quantitative evaluation of estimates of concentration response functions between urban air ultrafine particles and all-cause mortality and hospital admissions.

Introduction

Numerous studies have documented the effects of particulate matter air pollution on morbidity and mortality from respiratory and cardiovascular disease (*1, 2*). Most epidemiological studies have characterized particulate matter (PM) air pollution as the mass of particles smaller than 10 μm (PM_{10}) or 2.5 μm ($PM_{2.5}$). PM, however, is a complex mixture of ultrafine, fine, and coarse particles from a variety of sources. It has become increasingly clear that PM_{10} and $PM_{2.5}$ concentrations cannot capture the spatial and temporal variation of ultrafine particles (UFP) (*3*). In addition, much less information is available about the health effects of UFP. The first evidence of health effects related to exposure to ultrafine particles came from toxicological studies (*4, 5*). Seaton postulated that the number of UFP was a more relevant exposure metric than their mass, because of their larger surface area and their ability to penetrate into the interstitium (*6*). Subsequently, animal and human clinical studies have documented a variety of possible health effects of UFP exposure, including markers of respiratory and systemic inflammation (*4, 7*). The first epidemiological studies on UFP have been panel studies, which generally showed associations between short-term exposure to UFP and occurrence of acute respiratory symptoms and lung function (*8, 9*). However, few epidemiological studies have assessed more severe end points such as daily mortality and hospital admissions (*10, 11*). There are currently no epidemiological studies of long-term exposure to UFP.

Several reviews of the health effects of UFP have been published which focus particularly on physiological responses and potential biological mechanisms (*4*−*9*). However, a systematic quantitative analysis of the effect estimates has not been attempted in these reviews. In the systematic evaluation of the evidence of health effects of ambient air pollution by WHO in 2006, it was concluded that no quantitative summary of the effects of UFP could be made because of the paucity of data. As a consequence, health impact assessments (HIA) that include PM air pollution have not considered UFP in their evaluations but instead relied

* Corresponding author phone: 31 30 2539498; fax: 31 30 2539499; e-mail: g.hoek@uu.nl.
† Institute for Risk Assessment Sciences, University of Utrecht.
‡ Dutch National Institute for Public Health and the Environment (RIVM).
§ University of Birmingham.
|| Hogeschool Zuyd.
⊥ University Medical Center Utrecht.
University of Edinburgh Centre for Inflammation Research.
▽ Health Authority Rome.
○ University of Southampton.
◆ Institute of Inhalation Biology, Helmholtz Center Munich.
¶ K. U. Leuven.
+ National Public Health Institute.
@ University of Kuopio.
$ Napier University.
% Institute of Epidemiology, Helmholtz Center Munich.
& Ludwig Maximilians University.
= Copernicus Institute, University of Utrecht.

10.1021/es9021393

Published on Web 12/03/2009

upon PM_{10} or $PM_{2.5}$. This may be a serious limitation in HIA, particularly in relation to possible policies directed toward reducing motorized traffic emissions. Indeed, there is now evidence that the impact of motorized traffic on UFP is greater than on either PM_{10} or $PM_{2.5}$ concentrations (*12*−*14*). Thus, there is a need to establish concentration−response functions for effects of ultrafine particles on human health.

To this end, we have conducted an expert elicitation to address the possibility of specifying concentration−response functions for two key health end points from previous HIA's involving air pollution: mortality and hospital admissions. Expert elicitation was selected because of the limited amount of (epidemiological) studies for these end points, the methodological differences between existing studies, and the expectation that in the near future the number of studies will not increase rapidly (*15, 16*). As the limited published literature currently stands, we anticipated that a systematic literature review would not capture all available knowledge. The expert elicitation also allowed us to integrate knowledge from different relevant disciplines such as toxicology, epidemiology, and clinical medicine. Recently, two expert panel elicitations regarding health effects of $PM_{2.5}$ have been reported (*17, 18*). To allow comparison with the results of these studies, we broadly followed their design.

The goal of the expert elicitation was to synthesize the knowledge and opinions of experts from relevant disciplines on the potential health effects of ultrafine particles from atmospheric origin. More specifically, the following were our aims:

(1) To compare different possible causal pathways to describe the potential mechanisms by which ultrafine particles can lead to various health effects in humans and rate the likelihood of occurrence of these pathways.

(2) To derive quantified estimates of concentration response functions of UFP and selected health end points that can be used in HIA's, along with identification of the sources of uncertainties specific to concentration−response functions, qualitatively as well as, if possible, in a more quantitative way.

The results of the expert elicitation for the first aim have been published separately (*19*). This paper presents the quantitative estimates of the effect of UFP on human health, including evidence from both epidemiological and toxicological studies.

Experimental Section

Expert Panel Design. We limit the elicitation to UFP from atmospheric origin and did not discuss engineered nanoparticles. We also did not address the contribution of various sources of UFP to concentrations and personal exposure in detail, unless these affected the expert's estimates.

A protocol was developed a priori with the exact procedures of the elicitation, including the selection procedure of experts, the questions asked, the briefing book, and workshop procedures (Supporting Information). These experts had been invited through a two-stage systematic selection approach. In order to represent the different views in the environmental health field, we aimed to select five epidemiologists, five toxicologists, and five clinicians. The key questions presented to the experts were largely based upon the final questions of two previous expert panels on mortality effects of $PM_{2.5}$ (*17, 18*). The questions preceding the key question in these studies were not individually posed to the experts. The expert panel was invited for a two-day workshop in Utrecht, The Netherlands, for individual rating and group discussions (August 25 and 26, 2008).

Expert Panel Selection. We conducted a literature search to identify experts who had published peer-reviewed articles on UFP and health, using the following search terms: [ultrafine particles or particle number concentration or $PM_{0.1}$ or UFP] and [epidemiology or health or effects or toxicology]. We included literature published from 1995 until January 2008, using the bibliographic databases Pubmed and Scopus. 1995 was chosen as the start date because this was the year in which the hypothesis on mechanisms of health effects of ultrafine particles was published (*6*). Subsequently, we made a list of first, second, and last authors, ranked by the number of appearances. We selected authors if they had published at least two papers on UFP and health to serve as nominators. In addition, scientists who had participated in the WHO systematic review of air pollution and coordinators of EU projects in this research field (http://www.ec.europa.eu/research/) were included as nominators. We added these more generalist scientists as nominators to avoid potential bias related to being too enthusiastic about the effects of UFP. We approached the nominators by e-mail (including a brief outline of our planned expert panel) and asked them if they could provide us with the names of five toxicologists, five epidemiologists, and five clinicians who best met the general criteria adapted from ref *17*:

(1) Ideal experts should possess the educational background and/or experience both to display a thorough understanding of results from the *epidemiological and/or toxicological* literature addressing the relationship between UFP and various health effects and to evaluate these results in the context of other evidence pertinent to transport-related air pollution and various health effects issues.

(2) Experts may include primary scientific researchers as well as prominent individuals from scientific partners, institutions, journal editorial boards, and other such groups who, through their educational background and experience, are in a position to carefully interpret the key evidence regarding UFP and various heath effects.

(3) The nominees should all be based in Europe (for budgetary reasons).

One field of expertise was deemed sufficient, as it would have been very difficult to find scientists who are experts in toxicology and epidemiology. We identified 126 nominators of whom 43 subsequently responded after one reminder. We have no information on the reasons for nonresponse. We invited the five most nominated scientists within each discipline. Within a discipline, two experts could not be from the same institution. There were 9 toxicologists, 8 clinicians, and 10 epidemiologists nominated by five or more nominators. Invited experts who were unwilling or unable to participate were replaced by the next candidate within their discipline, provided the latter had been nominated by at least 5 nominators. Five experts (one epidemiologist, one toxicologist, and three clinicians) declined participation, because of time constraints. Some nominees commented that especially the distinction between clinician and toxicologist was not always sharp. Fourteen experts accepted the invitation. In the week before the meeting, one epidemiologist and one toxicologist withdrew from participation of the workshop for valid reasons. The final list of experts was: P. Borm, K. Donaldson (day 1 only), W. G. Kreyling, V. Stone (toxicologists); B. Brunekreef, F. Forastiere, J. Pekkanen, H.-E. Wichmann (epidemiologists); J. Ayres, S. Holgate, B. Nemery, and A. Seaton (clinicians).

Briefing Book. The briefing book (Supporting Information) was prepared by the research team from the University of Utrecht and RIVM though a review of the literature on studies of health effects of UFP. The briefing book consisted of a reading guideline including a tabular presentation of epidemiological studies of various end points (Supporting Information, Tables S1−S3) and a reference list of 81 papers. PDFs of the papers were temporarily made available to the experts on a password-protected Web site. Papers covered the following topics: reviews (epidemiological, toxicological, mechanisms); individual epidemiological studies on mortal-

ity, hospital admissions, lung function and symptoms and other cardiovascular outcomes; proximity to major roads studies; animal studies; human experimental studies; exposure assessment; and $PM_{2.5}$ expert panel elicitation studies. The number of epidemiological studies identified was small: five for mortality, four for respiratory hospital admissions, and five for cardiovascular hospital admissions. Twelve of these studies were from Europe and two from the US. We further included seven panel studies on lung function and 13 human and nine animal toxicology studies. We also included a derivation of the potential quantitative effect of long-term exposure to UFP on mortality, based upon epidemiological studies that assessed the impact of living near major roads, monitoring studies of UFP near major roads, and various assumptions regarding the fraction of the proximity effect that is due to UFP. Delfino and co-workers have similarly argued that some of the effect of more commonly measured pollutants (NO_2, CO) may be due to UFP (*7*). This derivation was added because of the complete lack of studies that actually measured UFP and the importance of not ignoring the potential long-term effects (Supporting Information, Table S4).

Workshop Structure. The workshop proceeded in three major steps: group discussion of questions and methods, individual rating, and group discussion of initial rating.

First, the overall purpose of the expert elicitation was presented. We specifically stated that our aim was not to arrive at consensus, as characterization of the variability of estimates was considered more informative. A presentation of potential biases in expert panels was given in order to limit their occurrence. The questions included in the protocol (Supporting Information) were discussed with the experts to make sure they were answering the same question. Our normative expert (J.v.d.S.) who had specific expertise in conducting expert elicitations provided a clarification of how probability functions can be specified using the interval method. The experts were first asked to specify the minimum and maximum effect they considered likely, similar to the US expert panel elicitation (*18*). Next, the likely shape of the distribution had to be conceptualized. Then, the 50th percentile was specified as the value for which larger/smaller effects are equally likely. The 25th and 75th percentiles had to be specified similarly. Experts were also instructed about what we expected them to take into account (conditioning issues) in their ratings, namely, causality, mechanisms, short-term and long-term exposure, shape of the exposure response function, biases in studies, and other indicator pollutants.

Experts developed initial estimates for the minimum, fifth, 25th, 50th, 75th, and 95th percentiles, and maximum estimate individually. Printed copies of the briefing book guidelines, summary tables S1−S3 (Supporting Information) and the original papers were available for reference. Written motivation for the rating was also asked for, both for intrinsic interest and because this tends to improve quantitative estimates (*15*).

The initial responses were collected and graphically presented to the group. Two moderators (J.v.d.S., G.H.) knowledgeable on expert panel elicitation and the subject matter, respectively, invited discussion aimed at clarifying differences in assessment between experts. We focused on high and low central estimates and uncertainty to obtain the rationale behind these estimates and provoke discussion about the plausibility. We did not cross-check responses to different end points. Experts were finally offered the option to revise their initial response.

Questions. The wording of the key question was:

What is your estimate of the true percent change in annual, all-cause mortality in the general EU population resulting from a permanent 1000 particles/cm^3 reduction in annual average UFP across Europe (given a population-weighted baseline concentration of 20 000 particles/cm^3)? In formulating your answer, please consider mortality effects of both reductions in long-term and short-term exposures.

A decrement of 1000 particles/cm^3 was selected as this is a change relative to average urban background concentrations that is broadly comparable to the 1 $\mu g/m^3$ decrement of $PM_{2.5}$ evaluated in the two expert panel elicitations (*17, 18*). European urban background concentrations of UFP are typically between 10 000 and 20 000 particles/cm^3. Urban background concentrations of $PM_{2.5}$ typically are between 10 and 20 $\mu g/m^3$. A more thorough comparison between the pollutants is hampered by the lack of data on spatial variability of UFP.

The key question had to be further clarified. First, experts were asked to provide estimates for differences in concentration at the *urban background*. Concentrations at urban background locations may differ from *personal exposure* to UFP. Because differences between urban background and personal exposure have affected the epidemiological studies used for assessment as well, no corrections of effect estimates from epidemiological studies were made. Second, all-cause mortality was interpreted as all natural cause mortality (i.e., excluding trauma deaths). Third, the quantitative questions were considered unconditional on the assessment of causality. Thus, if an expert attached a low likelihood to causality, the expert should provide lower quantitative effect estimates rather than assume causality.

The key question listed above was also asked for respiratory and cardiovascular hospital admissions. For the mortality effects, additional questions were asked regarding the importance of specified potential sources of uncertainty. In addition, experts were asked to provide a rating of the likelihood that the health effects of UFP differ between particles of different sources/composition, using the "level of confidence scheme" used by the Intergovernmental Panel on Climate Change (IPCC) (*20*).

Data Analyses. The main analysis of the data consisted of graphical displays of the distributions of the quantitative estimates of the individual experts. Calculation of summary estimates is controversial in expert panels, as evidenced in the two recent $PM_{2.5}$ expert elicitations: one study did not provide summary estimates (*18*) and the other provided different combinations including simple means assigning equal weight to each expert (*17*). We calculated summary estimates using simple medians of the individual estimates, attaching equal weights to each expert. We did not weigh with the inverse of the width of the distribution as is common in meta-analysis, because a larger uncertainty provided by an expert does not imply that the estimate is less informative. An advantage of the simple median is its transparency, compared to the more complicated estimates based on the full probability distributions.

Results

Mortality Effect Estimates. The distribution of the estimated effect of UFP on all-cause mortality is shown in Table 1 and Figure 1. Substantial variability is evident between the experts in median estimates and in their uncertainty (range of ratings). The median provided by most experts varied between 0.1 and 0.4%, with three experts providing higher estimates. The overall median was 0.30%. None of the experts excluded the possibility that UFP had no effect, as all provided a minimum of 0%. However, they did not consider this possibility very likely, as the fifth percentile was estimated as nonzero by seven of the experts. The experts used different methods to derive their estimates. Five experts based their estimates upon short-term studies of UFP, with most of them using the Stolzel et al. study (*11*) as the basis, because of the absence of actual long-term exposure UFP studies. These experts did not specifically state that they believed that long-

TABLE 1. Distribution of Estimated Percentage Decrease in All-Cause Mortality Associated with a Decrease of 1000 particles/cm^3 Ultrafine Particles[a]

	expert	min	P5	P25	P50	P75	P95	max
epidemiologists	1	0.00	0.00	0.01	0.10	0.15	0.30	0.60
	2	0.00	0.00	0.08	0.15	0.20	0.25	0.50
	3	0.00	0.10	0.20	0.30	0.40	0.50	0.50
	4	0.00	0.00	0.60	1.20	1.80	2.40	3.00
toxicologists	5	0.00	0.10	0.20	0.25	0.50	0.75	1.00
	6	0.00	0.20	0.30	0.40	0.70	0.90	1.00
	7	0.00	0.10	0.50	1.00	1.50	2.50	3.00
clinicians	8	0.00	0.05	0.10	0.20	0.50	0.70	1.00
	9	0.00	0.00	0.20	0.30	0.60	1.00	1.20
	10	0.00	0.10	0.30	0.60	0.90	1.10	1.20
	11	0.00	0.10	0.15	0.25	0.35	0.90	1.00
	median	0.00	0.10	0.20	0.30	0.50	0.90	1.00

[a] Min is minimum; P5 is the fifth percentile, P25 is the 25th percentile, etc.; max is maximum. Overall median is the simple median of the experts' median estimate. Experts 5, 6, 8, 9, and 11 assessed short-term effects; the other experts assessed long-term effects.

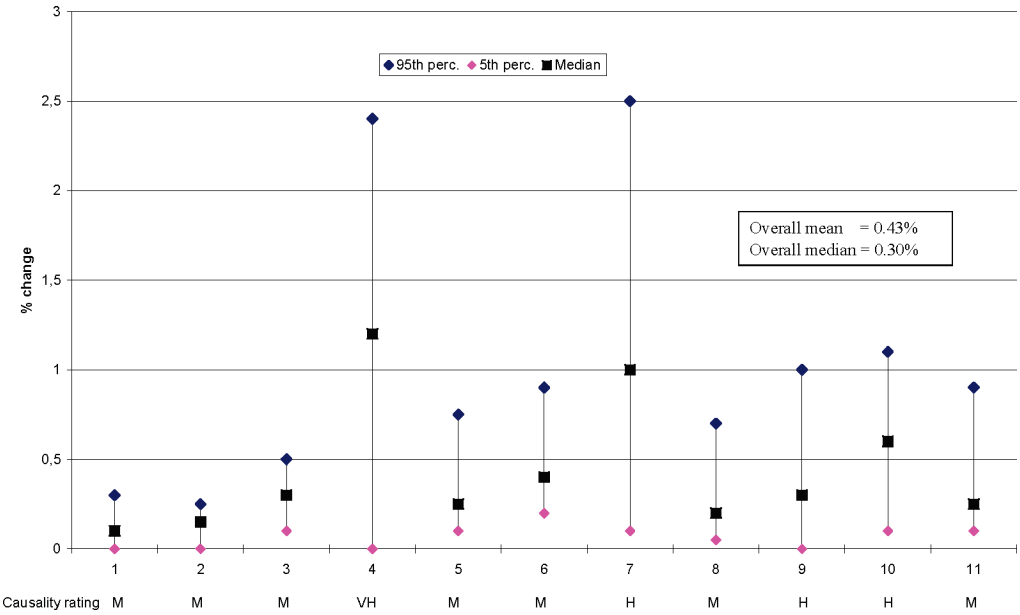

FIGURE 1. Distribution of estimated percentage decrease in all-cause mortality associated with a decrease of 1000 particles/cm^3 ultrafine particles. Experts 1–4 are epidemiologists, 5–7 toxicologists, and 8–11 clinicians. Overall median is the simple median of expert's median estimate. Causality ratings: M = medium, H = high, VH = very high.

term effects were less important. The three experts with the highest estimates first established the best estimate based upon the short-term study by Stolzel et al. (*11*). They then multiplied their estimate by six based upon the comparison of effect estimates for long-term and short-term exposure to $PM_{2.5}$, which they assumed to be 1% per 10 μg/m (*3*) for short-term and 6% per 10 μg/m^3 for long-term exposure studies, based upon the ACS study (*21*). These short-term estimates are actually higher than observed in large multicity studies such as APHEA-2 and NMMAPS (*1*), but the experts did not want to use a higher number to convert their UFP effect estimates. These experts made the assumption that the ratio of long-term to short-term effects is the same for $PM_{2.5}$ and UFP. Two experts used the traffic proximity studies (Supporting Information) as the basis for their assessment. One expert made use of the $PM_{2.5}$ study by Pope et al. (*21*) and made assumptions about the contribution of traffic PM to this association, viewing UFP especially as a marker of traffic PM. The mean of the central estimates was 0.56% and 0.29% for the experts assessing long-term versus short-term studies, respectively.

Experts considered right-skewed probability distributions the most likely and all considered it possible though not likely that the effect was zero. The development of the range in estimates differed with the method used to make estimates, e.g. experts 2 and 3 who used the traffic proximity studies used the various percent contributions of UFP to the road proximity effects in Table S5 (Supporting Information), along with an assessment of exposure issues. The experts assessing short-term effects took the 95% confidence interval of the studies in Table S1 (Supporting Information) as the basis of their assessment and adapted these based upon other (mechanistic) studies.

There were no striking differences in effect estimates between the three disciplines. There was a difference in derivation method of effect estimates, as all four epidemiologists and only one toxicologist and one clinician took into account long-term studies. The uncertainty of three of the epidemiologists was smaller than of the other experts.

The experts' estimate of the magnitude of effect was consistent with the assessment of the likelihood of causality (Figure 1). For the five experts who considered the probability

of causality to be high or very high, the median effect estimate ranged between 0.25 and 1.2%. For the six experts considering causality moderately likely, effect estimates ranged between 0.1 and 0.4%. Experts were instructed to provide effects estimates unconditional on causality.

Sources of Uncertainty. The experts indicated that the lack of studies on long-term exposure to UFP contributed significantly to the uncertainty about the quantitative relationship between UFP and all-cause mortality (Supporting Information Figure 1). All experts rated this uncertainty as being high or very high. The limited number of epidemiological studies was also rated as an important factor (high/very high ratings by eight experts) contributing to overall uncertainty. Six experts attached high/very high ratings to exposure misclassification as a source of overall uncertainty, with an additional three giving medium ratings. The quality and number of animal and human controlled exposure studies were generally not considered important factors contributing to the overall uncertainty.

Hospital Admissions. A full discussion of results is presented in the Supporting Information. Briefly, median effect estimates for *cardiovascular hospital admissions* were less variable between experts than for all-cause mortality (Supporting Information Figure 2). The overall median of the median rating was 0.20%. The experts were uncertain about the magnitude of the effect, as reflected by the wide distribution of their individual effect estimates. All experts specified a minimum of 0% and also the fifth percentile was generally very low (mean 0.02% with five experts including all epidemiologists specifying 0%).

Experts judged the uncertainty to be very large with respect to the effects of UFP on *respiratory hospital admissions* (Supporting Information Figure 3). The overall median of the median estimates was 0.16%. One (toxicological) expert refrained from making an estimate, because of the paucity of the data. This expert did provide estimates for CVD hospital admissions because of supporting evidence from end points on the causal pathway toward cardiovascular morbidity.

Discussion

An expert elicitation on the likelihood and quantification of health effects related to ultrafine particles in ambient air was held. Eleven European experts from the disciplines of epidemiology, toxicology, and clinical medicine were willing to quantify effects of UFP on all-cause mortality and to a lesser extent cardiovascular and respiratory hospital admissions. Substantial differences in the estimated UFP effect and its uncertainty were found between experts, though median responses were very similar for eight of the 11 experts. The estimated percentage decrease in all-cause mortality with a permanent 1000 particles/cm^3 decrease in UFP concentration ranged between 0.1 and 1.2%, with a median of 0.30%. The lack of studies of measured health effects of long-term exposure to UFP was rated as the most important factor contributing to the overall uncertainty. Estimation of effects on cardiovascular and respiratory hospital admissions was considered more uncertain compared to mortality.

The current paper reports on the first attempt to quantitatively synthesize the data and knowledge on health effects related to ultrafine particles. In 2006, the World Health Organization in its systematic review of ambient air pollution refrained from providing exposure response functions for UFP because of the limited number of studies then available (*2*). The experts judged the database of epidemiological studies and supporting studies as small but sufficient to provide estimates. A significant number of toxicological studies in animals and humans were used to complement the assessment based upon epidemiological studies. Toxicological studies played an important role in the assessment of causality (*19*) and in determining the uncertainty. The experts further evaluated near-roadway studies, which have shown large contrasts for especially ultrafine particles, to assess potential long-term effects of UFP. Because in the near future we do not expect to see a large increase in UFP studies, an assessment of the current UFP literature seems useful. Expert panels are especially useful when significant interpretation of the evidence is necessary, e.g., because the evidence base is relatively small.

Compared to previously published reviews, we added quantitative assessment of concentration−response functions and a more quantitative assessment of the likelihood of causality and causal pathways (*19*). The small number of epidemiological studies, the lack of studies on the effects of long-term exposure, and methodological differences between studies (e.g., in health end points considered) all required significant interpretation and integration of knowledge from experts, which is not easily included in a systematic review. The differences in assessment between experts illustrate the importance of assessment by a group of experts rather than relying on a single expert estimate.

Expert elicitations may be affected by various problems, such as selection of the expert panel, cognitive biases such as overconfidence and anchoring, and synthesis of estimates across experts (*15*).

We managed to assemble a large group of top-ranked European experts. In a recent workshop, it was discussed that the optimal size of an expert panel is between six and 12 (*16*). Though our panel was selected using a systematic approach, we cannot claim that the opinions of the experts are a random sample of the opinions in the entire scientific community. Because expert panels are typically small, this limitation applies, however, to all expert panels. We attempted to increase the variability in opinions, by specifically selecting experts from different disciplines (epidemiology, toxicology, clinical medicine) and by using peer-nomination.

Selection bias may have occurred because all experts have published on ultrafine particles. However, their research interest is much broader. Most experts should probably be classified as generalists. Four of the 11 experts were coauthors in the papers included in the Supporting Information (Tables S1−S3) on mortality and hospital admissions. Their estimates for mortality ranged from 0.1 to 1.2, thus covering the full range in the panel. This suggests that our findings were not unduly influenced by having study coauthors among the panelists. The potential for this type of bias is probably inherent to expert panels; e.g., in the Roman et al. $PM_{2.5}$ paper (*18*), most panelists contributed to the major US cohort studies.

We limited the elicitation to European experts for budgetary reasons. Non-European scientists were approached as nominators, and literature from outside Europe was included. Because most epidemiological research was done within Europe, the panel consisted of epidemiologists who performed studies on ultrafine particles. The two $PM_{2.5}$ expert panels were also geographically restricted to Europe (*17*) or the US (*18*).

We attempted to reduce cognitive biases, by specifically addressing them in the briefing document and at the start of the expert elicitation sessions. We have provided the experts with an example of subjective probability assessment, and we have asked for written motivation of the estimates in addition to the group discussions. The provision of tables of effect estimates of epidemiological studies on mortality and hospital admissions, including summary estimates, may have resulted in "anchoring" (*15*). Experts indeed indicated that they made use of these tables extensively, including the summary estimates. However, they clearly interpreted the information; e.g., they did not use the summary estimate for mortality but instead used the estimate from the one study

on all-cause mortality and used the other studies on cause-specific mortality as supporting evidence. Though we provided a derivation of long-term exposure effects of UFP (Appendix 2, Supporting Information), only two of the experts used this approach. Further, the probability distributions provided by most experts allowed for much larger potential effects than the (statistical) confidence intervals of the summary estimates calculated from the individual studies. Hence, we do not think the information provided has strongly affected the outcome of the elicitation. We have added summary tables, because we considered this as the common starting point for an assessment of concentration−response functions.

The difference in estimates between experts and the uncertainty expressed by each expert support the need for further research on the health effects of ultrafine particles. A key source of uncertainty that was identified by the experts was the lack of studies on long-term exposure to UFP. Such direct epidemiological studies are currently hampered by the difficulties in obtaining spatially resolved estimates of long-term exposure. Studies have shown higher spatial variability for UFP than for fine particles, largely related to proximity to traffic (*12*−*14*). Epidemiological studies therefore cannot adopt the approach of the US $PM_{2.5}$ studies (*21*) that relied on single or a few central monitoring sites to characterize exposure in a city. The high cost of particle number monitoring equipment prohibits large-scale monitoring, however. There is thus an urgent need for the development of more affordable monitoring equipment. Additionally, development of models that predict spatial patterns of UFP is needed.

Comparison with Previous Expert Panels on $PM_{2.5}$. The expert selection procedure, briefing book, and wording of the final questions were similar to two recent expert panel elicitations on $PM_{2.5}$ (*17, 18*). Our approach differed, in that we used fewer questions and group discussions combined with individual rating instead of the individual, structured interviews conducted in the $PM_{2.5}$ studies. Compared to the previous studies, we did not specifically ask the experts to answer the conditioning questions which in the individual interviews led to the final question. This may have made it more difficult to answer the key question. However, an introduction was given of the topics to be included in the assessment, and further group discussions were stimulated to provide reasons for differences between effect estimates. In the US elicitation study, it was noted that the panel included more epidemiologists than toxicologists (*18*). The European panel (*17*) also consisted of more epidemiologists. As we used a discipline-stratified selection procedure and stressed knowledge of toxicology as well as epidemiology, our panel was more balanced across these disciplines. In addition, we invited experts from clinical medicine with expertise in studies on environmental health.

Individual central estimates of UFP mortality effects ranged between 0.1 and 1.2% per 1000 particles/cm (*3*) in our panel. In the US $PM_{2.5}$ study, the central estimates varied between 0.6 and 2% (*18*) and in the European $PM_{2.5}$ study between 0.6 and 1.3% (*17*). Our estimates therefore varied more than for $PM_{2.5}$, probably due to the smaller database of epidemiological studies on UFP. Alternatively, the composition of the panel may have contributed to the difference, as there was no overlap with the US panel and limited overlap with the European panel. The uncertainty in terms of the range of plausible values estimated by our experts was also somewhat larger in our panel. Three of our experts specified a fifth percentile of 0 and one close to 0 (0.0002%), whereas the fifth percentile in the $PM_{2.5}$ studies was above 0 for all six experts (*17*) and 11 out of 12 experts (*18*). This is consistent with the lower rating of the likelihood of causality of UFP associations in our panel compared to the $PM_{2.5}$ associations in the US study (*18*). Further, the ratio of the 95th percentile to the median was somewhat larger than in the US PM2.5 study (*18*). The uncertainty distribution of three of the epidemiologists was smaller than that of the toxicologists and clinicians, for which we do not have a good explanation other than a different method to derive estimates.

Application in Health Impact Assessment? The estimates provided in this paper could be used to include UFP in HIA's of, for example, a certain policy scenario involving the reduction of traffic-related air pollution. The traffic contribution to ambient UFP concentrations is substantially larger than to PM_{10} and $PM_{2.5}$, as is the anticipated impact of traffic-related policies on UFP concentrations. The median effect size for UFP of 0.3% decrement in all-cause mortality in the general population associated with a 1000 particle/cm^3 decrement is comparable to the commonly used effect size for $PM_{2.5}$. The effect of a 1 $\mu g/m^3$ change in $PM_{2.5}$ concentration calculated from the largest cohort study (*21*) is 0.6%.

Hence, the outcome of the assessment may be different when a more traffic-specific PM fraction such as UFP is evaluated.

The current paper can be used to provide plausible values for the concentration−response function. The variability of effect estimates stresses the need to perform systematic sensitivity analyses, including a range of different assumed effect estimates. Whether it is worthwhile to include UFP in a specific HIA, depends among others on an evaluation of the anticipated impact of a policy on concentrations/exposures and the uncertainty of the concentration−response function.

Inclusion of health effects related to UFP in a HIA may lead to "double-counting" if some of the UFP effect is already included in the $PM_{2.5}$ effects and effects of UFP and $PM_{2.5}$ are added. The problem can be avoided by using UFP instead of $PM_{2.5}$ as a marker of the complex mixture of ambient particulate matter. Further, various studies have documented a low *temporal* correlation in the atmosphere between particle mass and number (*3, 22*). Hence, adding short-term effects of $PM_{2.5}$ and UFP likely better represents the effect of the complex PM mixture than the single effect estimates of each PM indicator. There is no empirical information on the *spatial* correlation of long-term average concentration of $PM_{2.5}$ and UFP, but this is likely higher related to similar sources. Adding long-term effects likely leads to (some) double-counting.

Acknowledgments

We acknowledge the contribution of Prof. A. Seaton, who elected from the onset not be a coauthor. The study was performed within the framework of EU 6th Framework study INTARESE and the strategic research project IQARUS of the Dutch National Institute for Public Health and the Environment). None of the authors has any financial or nonfinancial competing interest with the paper.

Supporting Information Available

More detailed information on mortality effects and the results for hospital admissions are included here. The detailed protocol and briefing book provided to the experts are also included here. This information is available free of charge via the Internet at http://pubs.acs.org/.

Literature Cited

(1) Pope, C. A., III; Dockery, D. W. Health effects of fine particulate air pollution: Lines that connect. *J. Air Waste Manage. Assoc.* **2006**, *56*, 709–742.
(2) WHO. *Air Quality Guidelines, Global Update* 2005; WHO Regional Office for Europe: Copenhagen, 2006.
(3) Pekkanen, J.; Kulmala, M. Exposure assessment of ultrafine particles in epidemiologic time−Series studies. *Scand. J. Work Environ. Health* **2004**, *30* (2), 9–18.

(4) Donaldson, K.; Stone, V.; Seaton, A.; MacNee, W. Ambient particle inhalation and the cardiovascular system: Potential mechanisms. *Environ. Health Perspect.* **2001**, *109* (4), 523–527.
(5) Oberdorster, G.; Oberdorster, E.; Oberdorster, J. Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. *Environ. Health Perspect.* **2005**, *113*, 823–839.
(6) Seaton, A.; MacNee, W.; Donaldson, K.; Godden, D. Particulate air pollution and acute health effects. *Lancet* **1995**, *345*, 176–178.
(7) Delfino, R. J.; Sioutas, C.; Malik, S. Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. *Environ. Health Perspect.* **2005**, *113*, 934–946.
(8) Ibald-Mulli, A.; Wichmann, H. E.; Kreyling, W.; Peters, A. Epidemiological evidence on health effects of ultrafine particles. *J. Aerosol Med.* **2002**, *15*, 189–201.
(9) Wichmann, H.; Peters, A. In *Ultrafine Particles in the Atmosphere* Brown L. M., Collings, N., Harrison, R. M., Eds.; Imperial College Press: London, 2003; pp 243−267.
(10) Wichmann, H. E.; Spix, C.; Tuch, T.; Wolke, G.; Peters, A.; Heinrich, J.; Kreyling, W. G.; Heyder, J. Epidemiological evidence of the effects of ultrafine particle exposure. *Res. Rep. Health Eff. Inst.* **2000**, *5*−*86*, 87–94, discussion.
(11) Stolzel, M.; Breitner, S.; Cyrys, J.; Pitz, M.; Wolke, G.; Kreyling, W.; Heinrich, J.; Wichmann, H. E.; Peters, A. Daily mortality and particulate matter in different size classes in Erfurt, Germany. *J. Expo Sci. Environ. Epidemiol.* **2007**, *17*, 458–467.
(12) Zhu, Y.; Hinds, W. C.; Kim, S.; Sioutas, C. Concentration and size distribution of ultrafine particles near a major highway. *J. Air Waste Manage. Assoc.* **2002**, *52*, 1032–1042.
(13) Cyrys, J.; Stolzel, M.; Heinrich, J.; Kreyling, W. G.; Menzel, N.; Wittmaack, K.; Tuch, T.; Wichmann, H. E. Elemental composition and sources of fine and ultrafine ambient particles in Erfurt, Germany. *Sci. Total Environ.* **2003**, *305*, 143–156.
(14) Lianou, M.; Chalbot, M. C.; Kotronarou, A.; Kavouras, I. G.; Karakatsani, A.; Katsouyanni, K.; Puustinnen, A.; Hameri, K.; Vallius, M.; Pekkanen, J.; Meddings, C.; Harrison, R. M.; Thomas, S.; Ayres, J. G.; Brink, H.; Kos, G.; Meliefste, K.; de Hartog, J. J.; Hoek, G. Dependence of home outdoor particulate mass and number concentrations on residential and traffic features in urban areas. *J. Air Waste Manage. Assoc* **2007**, *57*, 1507–1517.
(15) Slottje P.; van der Sluijs, J. J.; Knol, A. B. Expert elicitation: Methodological suggestions for its use in environmental health impacts assessments. RIVM letter report 630004001/2008; 2008 (http://www.rivm.nl/bibliotheek/rapporten/630004001.pdf).
(16) Cooke, R. M.; Probst, K. N. dutiosc.twi.tudelft.nl/…/ProbstCookeConfReport.FINAL081606.doc, 2006.
(17) Cooke, R. M.; Wilson, A. M.; Tuomisto, J. T.; Morales, O.; Tainio, M.; Evans, J. S. A probabilistic characterization of the relationship between fine particulate matter and mortality: Elicitation of European experts. *Environ. Sci. Technol.* **2007**, *41*, 6598–6605.
(18) Roman, H. A.; Walker, K. D.; Walsh, T. L.; Conner, L.; Richmond, H. M.; Hubbell, B. J.; Kinney, P. L. Expert judgment assessment of the mortality impact of changes in ambient fine particulate matter in the U.S. *Environ. Sci. Technol.* **2008**, *42*, 2268–2274.
(19) Knol, A. B.; de Hartog, J. J.; Boogaard, H.; Slottje, P.; van der Sluijs, J. P.; Lebret, E.; Cassee, F. R.; Wardekker, J. A.; Ayres, J. G.; Borm, P. J.; Brunekreef, B.; Donaldson, K.; Forastiere, F.; Holgate, S. T.; Kreyling, W. G.; Nemery, B.; Pekkanen, J.; Stone, V.; Wichmann, H. E.; Hoek, G. Expert elicitation on ultrafine particles: likelihood of health effects and causal pathways. *Part. Fibre Toxicol.* **2009**, *6*, 19.
(20) IPCC. Guidance notes for lead authors on the IPCC fourth assessment report on addressing uncertainty. http://ipcc-wg1.ucar.edu/wg1/Report/AR4_UncertaintyGuidanceNote.pdf, 2005.
(21) Pope, C. A., 3rd; Burnett, R. T.; Thun, M. J.; Calle, E. E.; Krewski, D.; Ito, K.; Thurston, G. D. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA, J. Am. Med. Assoc.* **2002**, *287*, 1132–1141.
(22) Sioutas, C.; Delfino, R. J.; Singh, M. Exposure assessment for atmospheric ultrafine particles (UFPs) and implications in epidemiologic research. *Environ. Health Perspect.* **2005**, *113*, 947–955.

ES9021393