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SCIENTIFIC CONTRIBUTION

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Abstract Homeopathy is controversial and hotly debated. The conclusions of systematic reviews of randomised controlled trials of homeopathy vary from 'comparable to conventional medicine' to 'no evidence of effects beyond placebo'. It is claimed that homeopathy conflicts with scientific laws and that homoeopaths reject the naturalistic outlook, but no evidence has been cited. We are homeopathic physicians and researchers who do not reject the scientific outlook; we believe that examination of the prior beliefs underlying this enduring stand-off can advance the debate. We show that interpretations of the same set of evidence—for homeopathy and for conventional medicine—can diverge. Prior disbelief in homeopathy is rooted in the perceived implausibility of any conceivable mechanism of action. Using the 'crossword analogy', we demonstrate that plausibility bias impedes assessment of the clinical evidence. Sweeping statements about the scientific impossibility of homeopathy are themselves unscientific: scientific statements must be precise and testable. There is growing evidence that homeopathic preparations can exert biological effects; due consideration of such research would reduce the influence of prior beliefs on the assessment of systematic review evidence.

Keywords Homeopathy · Plausibility · Bias · Pre-trial belief · Randomised controlled trial · Review

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Introduction

Homeopathy is a controversial form of complementary and alternative medicine (CAM). It has a history of over 200 years and global distribution, yet remains highly contentious. According to Hansen and Kappel (2012), members of the 'homeopathic community' hold beliefs which "while sincerely held with strong conviction, simply reject major parts of the naturalistic outlook". They go on to conclude that "there is no genuine reason to doubt the reasoning that leads us to reject the pre-trial beliefs of the homeopathic community". The statement concerning rejection of the naturalistic outlook is unreferenced.

The authors of the present paper are doctors and scientists with an interest in homeopathy, committed to the scientific method in researching and practising it. We are qualified in medicine and science and started practising these in conventional contexts, gradually becoming convinced that homeopathy is an effective option, supplementary to rather than conflicting with conventional medicine. We concur with Hansen and Kappel that the

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disagreement concerning the interpretation of reviews of randomised controlled trials (RCTs) is rooted in prior beliefs and their influence on the perception of evidence. We do not concur, however, with their assumption that the homeopathy community's positive view of the evidence is due to a rejection of the naturalistic scientific outlook. We ourselves, for example, do not reject any part of the naturalistic outlook. In this article, therefore, we take an overview of systematic reviews, meta-analyses and other reports on homeopathy and discuss the role of pre-trial or prior beliefs and plausibility bias in the divergent interpretation of the results reported.

Sometimes new evidence overturns theory, but sometimes not; the context is crucial. This has been expressed in terms of a crossword analogy (Haack 1998): the correctness of an entry in a crossword depends upon how well it is supported by the clue, whether it fits with intersecting entries, how reasonable those other entries are, and how much of the crossword has been completed. In this analogy, for homeopathy, the primary entry is: "Does it work (other than by placebo effects)?" The secondary intersecting entries are concerned with "How does, or could, it work?"

As yet, only the first entry (does it work?) has been discussed extensively; the intersecting entry (how does it work?) has too often been the subject of assumptions, despite the existence of a significant body of scientific research. The most controversial aspect of homeopathy, and the basis of the belief that the intersecting clues are incompatible with claimed efficacy, is its use of high dilutions, including 'ultramolecular' dilutions in which it is unlikely that any trace of the original substance remains. By definition, such dilutions cannot have any classical pharmacological action in vivo, since 'classical pharmacological action' is defined as interaction between pharmacologically active molecules and receptors.

It has been said that the claims made for homeopathy "wreck the whole edifice of chemistry and physics", that "they stand in clear opposition to conventional science" or "require a massive revision of standard chemistry and physiology" (Vandenbroucke and de Craen 2001; Sehon and Stanley 2010). We contend that these pronouncements are themselves unscientific.

It is against this background that the debate around homeopathy is conducted, and it accounts for the lack of consensus. Consistent with the naturalistic outlook, this paper suggests scientifically sound ways in which diverging views of homeopathy might be made to converge.

Overview of reviews and reports on homeopathy

To the surprise of many, three independent systematic reviews and meta-analyses of homeopathy published in leading medical journals between 1991 and 2000 reached essentially positive conclusions (Kleijnen et al. 1991; Linde et al. 1997; Cucherat et al. 2000). More recent reports, including those of the UK House of Commons Science and Technology Committee (STC) and the Belgian Federal Knowledge Centre for Healthcare (KCE), concluded that there is no proof of its effectiveness (Shang et al. 2005a, b; De Gendt et al. 2011; House of Commons 2010). This shift in conclusions is not accounted for by the impact of more recently published RCTs.

The first systematic review of homeopathy concluded: "Based on this evidence we would readily accept that homeopathy can be efficacious, if only the mechanism of action were more plausible" (Kleijnen et al. 1991). In 1997 Linde et al. published a new and independent meta-analysis, concluding that the results were not compatible with the hypothesis that the clinical effects of homeopathy are merely due to placebo (Linde et al. 1997). Vandenbroucke (1998) challenged the medical community to compare the forest plot of homeopathy trials in this analysis with a similar plot of conventional trials. Sterne, Egger and Davey Smith postulated quality bias as an explanation for a difference in efficacy despite similar forest plots (Sterne et al. 2001).

The only systematic review that attempted directly to compare homeopathy and conventional medicine was that of Shang et al. The funnel plots of homeopathy and conventional medicine showed no significant differences (see Fig. 1). For both plots there was a clear majority of trials suggesting an effect of verum over placebo and the proportions of positive results were similar. The initial hypothesis was that positive results were due to quality bias, especially in smaller trials, leading to increased asymmetry of the plot. This hypothesis was falsified: the quality of homeopathy trials was, in fact, superior to that of matched trials of conventional medicine: 19 % trials of homeopathy compared to 8 % of conventional medicine were of high quality.

The divergence of interpretation can be visualised from the plots of the results of RCTs for homeopathy and conventional medicine, which formed the basis of the negative Shang meta-analysis (Shang et al. 2005a, b). As Fig. 1 shows, the plots for homeopathy and conventional medicine are very similar; this is compatible with the conclusion of a previous systematic review that the evidence for homeopathy is not inferior to that for conventional medicine (Kleijnen et al. 1991; Vandenbroucke 1998). The hypothesis that this was due to quality bias (i.e. that the evidence for homeopathy is positively skewed by low quality positive RCTs) has been disproved.

The final conclusion of Shang et al. ("weak evidence for homeopathy and strong evidence for conventional medicine") was based on subsets ('larger high quality trials') of 8/110 homeopathy trials compared with 6/110 conventional

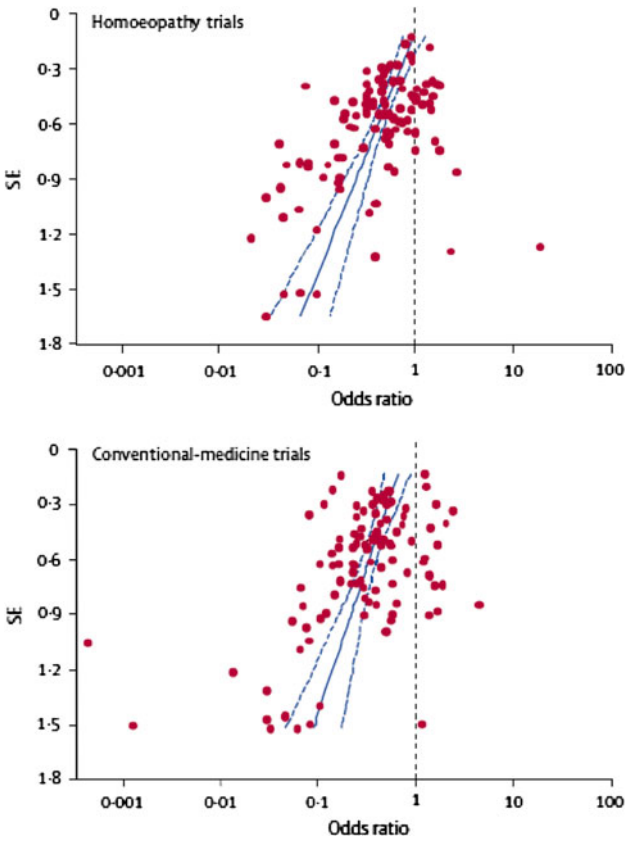

Fig. 1 Funnel plot comparing 110 homeopathy trials with 110 conventional trials, matched on indication. *Source*: Shang et al. 2005a, b. Reprinted from The Lancet 2005, with permission from Elsevier

trials. After publication of the review it became clear that similar medical conditions had not been compared (Table 1). And the criteria for 'good quality' were changed, resulting in the exclusion of a larger high-quality trial on seasonal allergic rhinitis showing considerable effect (Reilly et al. 1986; see Rutten and Stolper 2008).

It was known that better homeopathy trials yield less positive results (Linde et al. 1999), but this is also true for conventional medicine (Shang et al. 2005a; Schulz et al. 1995). This review concluded that larger high quality studies show less effect than comparable conventional studies, but in fact it could not rightly reach such conclusion, because the trials were not comparable: they were in different conditions (Table 1). Regrettably, these important facts were not revealed until well after publication. There is much heterogeneity and the outcome is highly sensitive to excluding trials previously classified as high quality and strongly influenced by a single indication (muscle soreness after marathon running) and the definition of 'larger trial' (Lüdtke and Rutten 2008).

Shang et al. did, however, identify a subset of eight trials of homeopathy for acute upper respiratory tract infections (URTI) with a "substantial beneficial effect (odds ratio 0.36, [95 % CI 0.26–0.50])" and no evidence of bias. But they went on to dismiss this because of "biases … shown by our study"—a surprising conclusion given that they had also shown that homeopathy studies were of higher quality and therefore less biased than those of conventional medicine.

The KCE review considered studies showing statistically non-significant trends as negative instead of as non-conclusive. For example, it states that Passalacqua "identified 10 RCTs on homeopathic treatment of allergic rhinitis and concluded that positive results were described in rhinitis with homeopathy in good quality trials, but that an equal number of negative studies counterbalance the positive ones" (De Gendt et al. 2011). In reality, Passalacqua identified five studies with no statistically significant difference between verum and placebo (mostly because the trials were statistically underpowered) and five that showed statistically significant effect of verum over placebo (Passalaqua et al. 2006). This method of analysis is known as 'vote counting', but it is a strange kind of vote

Table 1 Larger high-quality trials of eight homeopathy and six conventional medicine according to Shang's post-publication data

Indication	Homeopathy	Conventional medicine
Diarrhoea	Jacobs. N = 116	Kaplan. N = 256
Treatment of influenza	Papp. N = 334	Nicholson. N = 319
		de Flora. N = 248
Prevention of influenza	Rottey. N = 501	
Plantar warts	Labrecque. N = 162	
Weight loss.	Schmidt. N = 208	
Muscle soreness	Vickers. N = 400	
Headaches.	Walach. N = 98	
Sinusitis	Weiser. N = 104	
Stroke (venous)		Horn. N = 454
Upper genital tract infection		Crowley. N = 273
Seasonal allergy		Möller. N = 146

counting when abstentions are counted as votes against! In fact many of the votes labelled negative showed a positive trend which did not reach statistical significance; meta-analysis of such data might yield a positive pooled effect, and it is virtually impossible that it could have yielded a negative pooled effect.

Likewise, Bewley (2011) questioned the significance of eight positive trials out of 16 placebo controlled trials on respiratory tract infections. But conventional treatment of the same condition is equally vulnerable to this kind of analysis. Figure 2 shows a similar result for conventional trials of respiratory tract infections taken from Shang et al.: 9 out of 21 trials have statistically non-significant results (including three whose mean effect is negative). By the KCE's method, there would be no convincing evidence from Shang's paper for conventional medicine in respiratory tract infections! The homeopathy trials on URTI in Shang's comparison showed 11 out of 21 trials with statistically non-significant results (including two whose mean effect is negative: the other nine trials are merely non-conclusive). Negative and non-conclusive are not equivalent; if they are treated as such, neither conventional medicine nor homeopathy is effective for URTIs.

Non-conclusive often means a positive trend with insufficient statistical power. This is illustrated by three trials of homeopathy for diarrhoea in children (Jacobs et al. 1993, 1994, 2000): one showed a statistically non-significant inter-group difference, two showed a statistically significant difference; the pooled results were highly significant ($p = 0.008$). Meta-analyses of homeopathy for conditions including URTI and seasonal allergic rhinitis give similar results (Bellavite et al. 2006). For these conditions there is some heterogeneity between the included trials, but this is frequently the case in conventional medicine too.

The STC report focused almost exclusively on the meta-analysis of Shang et al., and ignored criticisms of this meta-analysis, other systematic reviews of homeopathy as a whole, homeopathy for specific conditions, or evidence concerning the possible mode of action of homeopathy. It was strongly criticised by a significant number of Members of Parliament (Early Day Motion 908, 2009).

Sources of prior and pre-trial belief

Not surprisingly, proponents of homeopathy tend to point to Linde's review, and opponents to Shang's review, to support their views (Hansen and Kappel 2012). Such lack of concordance between the results of systematic reviews and meta-analyses is not as unusual as one might suppose. After analysing 160 Cochrane reviews, Ezzo concluded: "The number of reviews indicating that modern biomedical interventions show either no effect or insufficient evidence is surprisingly high. Inter-rater disagreements suggest a surprising degree of subjective interpretation involved in systematic reviews" (Ezzo et al. 2001).

Vandenbroucke, Hansen and Sehon have all made sweeping but non-specific claims (mentioned in the "Introduction") that homeopathy is in conflict with fundamental scientific ideas (Vandenbroucke and de Craen 2001; Hansen and Kappel 2012; Sehon and Stanley 2010). Hansen and Kappel state that there is no reason to not reject the pre-trial belief of the homeopathic community because, allegedly, "they reject conventional science", but admit that the empirical question how pre-trial beliefs are formed is largely unexplored (Hansen and Kappel 2012).

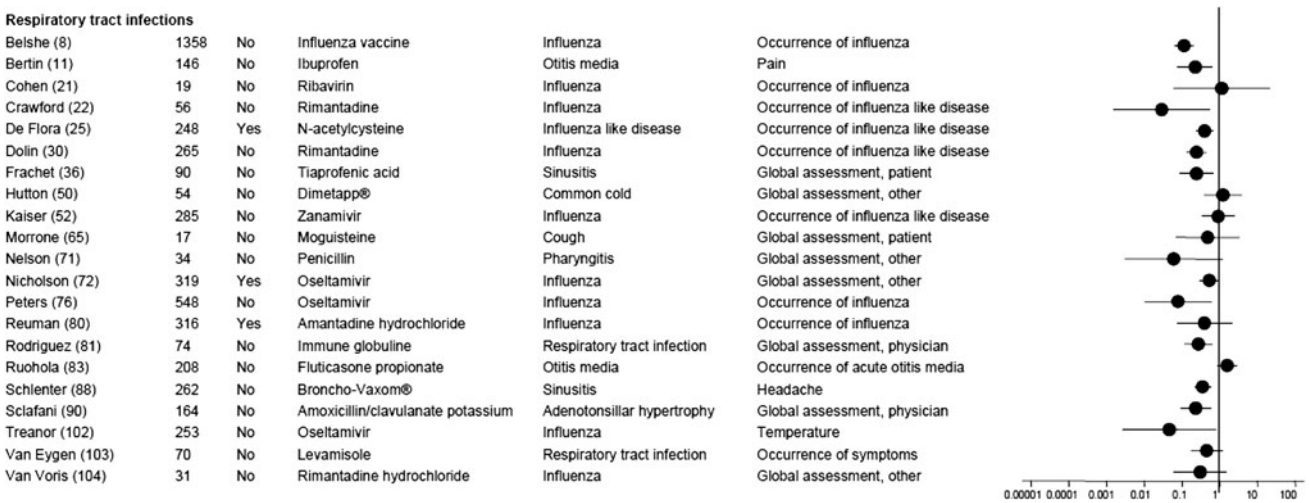

Fig. 2 Graphical presentation of effects and 95 % confidence intervals of conventional trials on respiratory tract infections matching existing homeopathy trials. *Source*: (http://www.ispm.ch/fileadmin/doc_download/1431.Study_characteristics_of_allopathy_studies_corrected.pdf)

There are obvious sources of pre-trial belief. These include well documented paradoxical low-dilution effects. The basic idea of homeopathy is the exploitation of the paradoxical secondary effects of low doses of drugs. Secondly, reverse or paradoxical effects of drugs and toxins in living organisms as a function of dose or time are very widely observed in pharmacology and toxicology. They are variously referred to as hormesis (the stimulatory or beneficial effects of small doses of toxins) hormligosis, Arndt-Schulz effects, rebound effects, dose-dependent reverse effects and paradoxical pharmacology (Calabrese and Blain 2005; Calabrese et al. 2006; Bond 2001; Teixeira 2007, 2011). This of course does not address the question of ultramolecular dilutions, but the majority of dispensed homeopathic medicines are not in the ultramolecular range (De Gendt et al. 2011).

Of course the most controversial aspect of homeopathy is its use of ultramolecular dilutions. But again this is not a scientific 'black hole' that we have filled with arbitrary beliefs, as Hansen and Kappel assume.

The HomBRex Database on Fundamental Research in Homeopathy (www.carstensstiftung.de/hombrex) includes details of about 1,500 basic research experiments in homeopathy. Of these, 830 experiments employed ultramolecular dilutions; in 745 of these at least one positive result was reported. A more recent meta-analysis evaluated 67 in vitro biological experiments in 75 research publications and found high-potency effects were reported in nearly 75 % of all replicated studies; however, no positive result was stable enough to be reproduced by all investigators (Witt et al. 2007).

The most repeated series of in vitro experiments in homeopathy is the model of the allergic response to antibody using the human basophil degranulation test. There are now 17 publications on inhibition of basophil activation by high dilutions of histamine, spanning over 25 years and including multi-centre and independent replications. There has been steady refinement of the method, including improved markers and the introduction of flow cytometry (Sainte Laudy and Belon 2009; Endler et al. 2010). There is a consistent peak at 16c (10^{-32} M), well into the ultramolecular range. These experiments have also yielded insights into possible mechanisms of action, for instance the response is highly specific to histamine; it is not induced by the structural analogue histidine, it appears to be mediated by H2 receptor-mediated inhibition of basophil activation and it is partly blocked by the H2 receptor antagonists ranitidine and cimetidine (Belon et al. 2004; Chirumbolo et al. 2009).

Another cellular system that has been the subject of repeated experiments over a long period of time is the effect of ultramolecular dilutions of aspirin on blood clotting (Eizyaga 2007). Recent work with 'knock-out' mice suggests that the effect is due to inhibition of COX-2 mediated PGI_2 production in vascular endothelium (Aguejouf et al. 2008).

The most robust whole animal model is the effect of thyroxine on the rate of metamorphosis of frogs. This effect has been reproduced in multi-centre experiments (Welles et al. 2007) and by independent workers with different species of frog and with different outcome measures (Guedes et al. 2004).

The other major source of our prior beliefs is practice experience. This may be regarded the lowest level of evidence, but it is under-rated by many (Vandenbroucke 2001). After adding homeopathy to conventional treatment, many unsuccessful cases improved (Marian et al. 2008). The repetitive character of such experiences gradually updated our belief, consistent with Bayesian theory (Rutten 2008).

Outcome and cohort studies support our belief in the real world effectiveness of homeopathy. For instance a multicentre, prospective, 'real world' observational study compared the effectiveness of homeopathy with conventional medicine. Thirty doctors at six clinical sites in four countries enrolled patients with acute respiratory problems. Response at 14 days was 82.6 % for homeopathy versus 68 % for conventional treatment. The rate of adverse events for conventional treatment was 22.3 %, versus 7.8 % for homeopathy (Riley et al. 2001).

In a prospective, multi-centre cohort study in Germany and Switzerland, 73 % of 3,709 patients contributed data with 8-year follow-up. The most frequent diagnoses were allergic rhinitis and headache in adults, atopic dermatitis and multiple recurrent infections in children. Disease severity decreased significantly ($p < 0.001$) between baseline, 2 and 8 years. Younger age, female gender and more severe disease at baseline correlated with better outcomes (Witt et al. 2008).

Discussion

Vandenbroucke and de Craen have pointed out that homeopathy touches a raw nerve and that the way we look at the 'other' may reveal much about ourselves (Vandenbroucke and de Craen 2001). This is apposite here: as we have shown, our prior beliefs are not arbitrary but are supported by a significant body of evidence. It is Hansen and Kappel's prior belief that homeopaths' views are non-naturalistic that is arbitrary and unsupported by evidence.

We have previously introduced the concept of plausibility bias as an explanation for neglect of evidence on the clinical effects of homeopathy (Rutten et al. 2010). Plausibility bias arises from one's agreement or disagreement with a proposition that has extant intellectual frameworks,

theories or prejudices; it may be positive or negative. We do not offer any new analysis of proof for homeopathy; we are attempting to make sense of the diverging and sometimes bitterly disputed interpretations of the evidence. Reviews have a subjective element and we are adherents of homeopathy. We could include other categories of evidence: for instance safety, not discussed here but a point in favour of homeopathy (Marian et al. 2008). Some of the larger studies in Shang's comparison were of conventional drugs subsequently withdrawn because of serious adverse effects (Rutten and Stolper 2008). But that is not our point: the wider discussion is degenerating into a sterile cycle of casting doubts on each other's results. We seek a route out of this impasse.

The divergence of opinions shows that falsifying the placebo hypothesis for homeopathy encounters serious problems. Mistrust in the evidence for homeopathy is primarily based on plausibility. Demanding RCTs to decrease disbelief (Hansen and Kappel 2010), and subsequently ignoring their results on grounds of the same disbelief, is circular reasoning. On the other hand, there is as yet no satisfactory explanation for the mechanism of action for homeopathy. Homeopathy is a problematic test case for evidence-based medicine (EBM); is EBM confined to 'plausible' medicine?

Prior beliefs cause asymmetry in the burden of proof: eight anonymous studies were sufficient for a Lancet editorial to declare 'The end of homeopathy' (Lancet 2005), but 110 studies of better quality than equivalent studies of conventional medicine do not suffice to enter a next level in the discussion (Shang et al. 2005a). There is also asymmetry in financial structure: the estimated costs to develop one conventional medicine are 2 billion euros, but sales more than counterbalance such costs. The costs to produce a sufficient explanation for homeopathy might be huge, but without protection of intellectual property such research will never be a sound investment for commercial interests.

Our prior beliefs about homeopathy do not originate from a theoretical concept like 'memory of water', but arise initially from personal clinical observations, supported by observational and cohort studies and reinforced by the results of RCTs and in vitro experiments. This is not uncommon in medicine: most therapies ultimately originate from practice experience. In some clinical domains, for instance recurrent URTI, homeopathy can attain the highest level of evidence (Shang et al. 2005a). The only argument against homeopathy in this case is'it doesn't work because it can't work'.

Reducing the problem

Does homeopathy really wreck the whole edifice of chemistry and physics? If this were the case we must distrust not only patients' experience and doctors practising both homeopathy and conventional medicine, but also RCT evidence. A more convenient solution would be to suppose that the edifice stays intact and an additional mechanism can be found that explains how homeopathy works.

To return to the crossword analogy: there is evidence for the primary entry (homeopathy is not merely a placebo effect). This seems incompatible with intersecting entries, particularly those concerning possible mechanisms of action of very high dilutions. There is evidence, with replication including in multicentre experiments and independent replications, that ultra-molecular dilutions can exert biological effects. The fact that the mediator of these effects is currently unknown is valid ground for scepticism but not for extreme, yet vague, claims that homeopathy overturns much of existing knowledge. The suggestion that the homeopathic preparation process might transmit information no more contradicts established scientific laws than does the storage of information, by physical rather than chemical processes, in a magnetic medium.

Conclusion

The disagreement around the interpretation of systematic reviews and meta-analyses is partly a function of plausibility bias. We have shown that it is an important factor in the interpretation of the results of RCTs of homeopathy and the source of much of the disagreement concerning the interpretation of systematic reviews and meta-analyses of such research.

Plausibility bias is necessary and probably unavoidable: in making decisions about our beliefs or courses of action we must take account of existing intellectual frameworks. However, plausibility bias can have a damaging effect on scientific progress and this is the case for homeopathy. To be admissible in scientific discourse, plausibility bias must itself be scientific. This means that it must be testable, which in turn requires that it must be explicit and precise. Sweeping generalisations about homeopathy 'wrecking whole edifices' or standing in opposition to conventional science etc. are unscientific: they are incapable of being tested. It is remarkable that their authors do not specify precisely why they believe that homeopathy has such apocalyptic implications for science. We are unaware of any contribution to the debate that has mentioned a single specific scientific law that is threatened by homeopathy. Hansen and Kappel's assertion that the homeopathic community rejects the naturalistic outlook is not evidence-based.

Plausibility bias has introduced more heat than light into the debate around homeopathy: it has fired the debate without illuminating its information content. We do not

deny that homeopathy raises major scientific issues, but we remain convinced that these will eventually be resolved by application of authentic scientific method, especially in the context of further in vitro experiments.

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