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# Replications of fundamental research models in ultra high dilutions 1994 and 2015 – update on a bibliometric study

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***Introduction:*** **This paper focuses exclusively on experimental models with ultra high dilutions (i.e. beyond $10^{-23}$) that have been submitted to replication scrutiny. It updates previous surveys, considers suggestions made by the research community and compares the state of replication in 1994 with that in 2015.**
***Methods:*** **Following literature research, biochemical, immunological, botanical, cell biological and zoological studies on ultra high dilutions (potencies) were included. Reports were grouped into *initial studies*, *laboratory-internal*, *multicentre* and *external* replications. Repetition could yield either *comparable*, or *zero*, or *opposite* results. The null-hypothesis was that test and control groups would not be distinguishable (zero effect).**
***Results:*** **A total of 126 studies were found. From these, 28 were initial studies. When all 98 replicative studies were considered, 70.4% (i.e. 69) reported a result comparable to that of the initial study, 20.4% (20) zero effect and 9.2% (9) an opposite result. Both for the studies until 1994 and the studies 1995–2015 the null-hypothesis (dominance of zero results) should be rejected. Furthermore, the odds of finding a *comparable* result are generally higher than of finding an *opposite* result. Although this is true for all three types of replication studies, the fraction of *comparable* studies diminishes from laboratory-internal (total 82.9%) to multicentre (total 75%) to external (total 48.3%), while the fraction of *opposite* results was 4.9%, 10.7% and 13.8%. Furthermore, it became obvious that the probability of an external replication producing comparable results is bigger for models that had already been further scrutinized by the initial researchers.**
***Conclusions:*** **We found 28 experimental models which underwent replication. In total, 24 models were replicated with comparable results, 12 models with zero effect, and 6 models with opposite results. Five models were *externally* reproduced with comparable results. We encourage further replications of studies in order to learn more about the model systems used.** *Homeopathy* (2015) **104**, 234–245.

**Keywords:** Review; Basic research; Homeopathy; Ultra high dilution; Replication

## Introduction

There are several thousand references on fundamental research in homeopathy, including hundreds of references on extreme dilutions. This paper focuses exclusively on experimental models with ultra high dilutions (i.e. beyond $10^{-23}$) that have been submitted to replication scrutiny.[1–101] It follows on from a previous survey of

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2009[102] which gave an overview of fundamental biochemical and biological studies that used high homeopathic potencies and that had been subjected to laboratory-internal, multicentre or external replication trials. Physicochemical or clinical studies were not included, nor studies on dilutions below $10^{-23}$, nor studies in relation to which no attempt of replication could be found in literature.

The studies under survey were grouped into broadly defined clusters according to the methodology employed (see below Methods).

Apart from being a mere update this paper considers suggestions made by the research community in response to the first publication[102] regarding the literature surveyed as well as its clustering, evaluation and discussion. It also compares the state of replication in 1994, when the anthology 'Ultra High Dilution' was published,[99] with that in 2015. Furthermore, with regard to the models presented, we tried to determine whether it makes sense to pursue laboratory-internal and multicentre replication research as a means of mitigating the probability of external replication studies producing zero results.

## Methods

### Literature search

Sources of information were reviews,[99,102–113] personal contact with members of the homeopathic research community, and the MEDLINE (www.PubMed.gov) and HOMBREX (www.carstens-stiftung.de) databases. Allowed literature sources were publications (in peer-reviewed and not peer-reviewed journals, book sections and books) as well as unpublished academic papers. As a rule, unpublished papers were disregarded wherever published papers on the same study were available. Especially from 2010 to 2015, we focused on PubMed listed publications. Although we have done what seemed possible to identify all relevant studies, the annotated bibliography presented here does not claim to be exhaustive.

### Inclusion criteria

We included biochemical, immunological, botanical, cell biological and zoological studies on ultra high, homeopathically prepared dilutions (potencies), i.e. ≥24x (=$10^{-24}$) or 12c (=$100^{-12}$). Studies published after 1940 were required to report evaluation of results by statistical methods (minimum requirement: mean or median, number n of samples, standard deviation or standard error, OR, number N of samples, level of significance of a statistical test).

To be included the experiment had to have been repeated. Replications were formally considered as such whenever it was possible to find

- at least two publications by the same initial working group, including a follow-up trial of an initial publication (laboratory-internal replication) or
- at least one publication reporting on a multicentre trial (independent experiments in different locations/laboratories, organized by one study coordinator, normally from the initial team), or
- at least one publication by the initial workgroup and one with external authorship, both dealing with the same experimental model.

Furthermore, replication was considered as such when a later study dealt with the same biological system and the same potentized substance as an earlier one. Within such clusters, however, a certain degree of deviation was accepted with regard to the biological system (e.g. the use of *Chlorella vulgaris* or *Chlorella pyrenoidosa*), the potency level (e.g. 25x or 30x) and potency type (decimal (x) or centesimal (c)) and the nature of the control (e.g. prepared step by step or not, succussed or not, or type not mentioned).

One and the same publication could refer to the results of more than one study. Where numbers of studies are quoted in connection with multicentre trials they refer to the number of trials in different locations/laboratories. Among the initial studies, one of the researchers involved was always considered as the 'initial' researcher. When their name could not be identified from the publication, the first author's name was mentioned. Apart from the main publications, four publications giving additional information were cited.[98–101]

Thus, we extracted all studies from the included publications and grouped them into experimental models.

Studies (i.e. initial and repeated studies) were further grouped according to results achieved:

- Initial studies: as an inclusion criterion to be candidates for replication trials, these had shown a significant difference between test and control group, e.g. enhancing growth
- Repeated studies, the results of which were *consistent* with the initial study, i.e. where a *comparable* result (in the same direction, e.g. enhancing growth) was found
- Repeated studies, where *no* difference between test and control group was found (zero effect)
- Repeated studies, the results of which were *opposite* to the initial study, i.e. when results were *different* in direction (e.g. decreasing instead of increasing).

The null-hypothesis was that test and control groups would not be distinguishable, i.e. there would be no result of treatment with the potency (zero effect). In this survey paper, we focused on a graphical representation of the data rather than statistical calculations. Raw data for further analysis are given in Table 1 (see Results).

## Results

A total of 126 studies were found. Figure 1 shows the proportion of models and studies.

Numbers of studies performed until 1994[102] and in the period from 1995 to 2015 were: on enzymes 2 + 7, on cultured cells 0 + 2, on plants 4 + 30, on immune cells 12 + 16, on isolated organs 0 + 4, on amphibians/fish 8 + 18 and on rats/mice 9 + 14.

**Table 1** Fundamental models and studies on ultra high dilutions. Studies were classified according to the type of replication (initial, laboratory-internal, multicentre, external) and to the results achieved (comparable, zero, opposite)

| | | | | |
|---|---|---|---|---|
| *biochemistry: enzyme diastase & mercury chloride* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Persson 1932 [1] | | | |
| *multicentre* | | | | |
| *external* | | | Bluth 2005 [2] | Boyd 1954 [3] |
| *resumee: increase of enzyme reaction in 1 study, decrease in 1, zero result in 1* | | | | |
| | | | | |
| *biochemistry: enzyme acid phosphatase & ubiqinone* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Harisch 1997 [4] | Harisch 1999 [5] | | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: decrease of enzyme reaction in both studies* | | | | |
| | | | | |
| *biochemistry: enzyme acid phosphatase & cAMP* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Harisch 1998 [6] | Harisch 1999 [7] | | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: decrease of enzyme reaction in both studies* | | | | |
| | | | | |
| *biochemistry: enzyme alpha amylase & mercury chloride* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Sukul 2002 [8] | | | |
| *multicentre* | | | | |
| *external* | | | Bluth 2005 [2] | |
| *resumee: increase of enzyme reaction in the initial study, zero result in the repetition* | | | | |
| | | | | |
| *cultured mammalian cells: neuroblastoma cells & tumour necrosis factor alpha* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Carmine 1997 [9] | | | |
| *multicentre* | | | | |
| *external* | | | Herberth 1999 [10] | |
| *resumee: increase of H202 production in the initial study, zero result in the repetition* | | | | |
| | | | | |
| *plants: algae Chlorella & copper sulphate* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Graviou 1971 [11] | | | |
| *multicentre* | | | | |
| *external* | | | Moss 1977 [12] | |
| *resumee: growth stimulation of poisoned algae in the initial study, zero result in the repetition* | | | | |
| | | | | |
| *plants: wheat seedlings & silver nitrate* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Kolisko 1926 [13] | | | |
| *multicentre* | | | | |
| *external* | | Pongratz 1994 [14] | Endler 1998 [15] | |
| | | Pongratz 1998 [15] | | |
| | | Nograsek 1998 [15] | | |
| *resumee: increase of stalk growth in 4 studies, zero result in 1 study* | | | | |
| | | | | |
| *plants: arsenic poisoned wheat seedlings & arsenicum album* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Betti 1997 [16] | Brizzi 2000 [17] | | |
| | | Brizzi 2005 [18] | | |
| | | Nani 2007 [19] | | |
| | | Brizzi 2011 [20] | | |
| *multicentre* | | | | |
| *external* | | | Lahnstein 2009 [21] | Binder 2005 [22] |
| | | | | Lahnstein 2009 [21] |
| *resumee: stimulation of growth and germination rate, decrease of variance in 5 studies,* | | | | |
| *decrease of growth and germination rate in 2 studies, increase of variance in 1 study* | | | | |
| | | | | |
| *plants: wheat seedlings (stalk growth) & gibberellic acid* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Pfleger 2008 [23] | Hofäcker 2008 [23] | | |
| | | Reich 2009 [24] | | |
| | | Hribar 2013 25 | | |
| *multicentre* | | | | Reischl 2009 [24] |
| | | | | Thieves 2009 [24] |
| *external* | | | | |
| *resumee: decrease of stalk growth in 4 studies, increase in 2* | | | | |
| *hypothesis: decrease in growth season, increase in winter* | | | | |
| | | | | |
| *plants: wheat seedlings (germination) & gibberellic acid* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Schiestl 2010 [26] | | | |
| *multicentre* | | Hartung 2010 [26] | Matzer 2012 [27] | Hofstätter 2012 [27] |
| | | Schwärzler 2012 [27] | Seunig 2012 [27] | |
| *external* | | | | |
| *resumee: decrease of germination in 3 studies, increase in 1 study, zero result in 1 study* | | | | |
| | | | | |
| *plants: duckweed & gibberellic acid* | | | | |

Table 1. *(Continued)*

| | | | | |
|---|---|---|---|---|
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Scherr 2009 [28] | | | Majewsky 2014 [29] |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: increase of growth in 1 study, decrease in 1* | | | | |
| | | | | |
| *plants: cress growth and biocrystallisation & stannum metallicum* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Andersen 2012 [30] | Andersen 2015 [31] | | |
| *multicentre* | | Doesburg 2012 [30] | | |
| | | Doesburg 2015 [31] | | |
| *external* | | | | |
| | | | | |
| *resumee: additive-specific crystallisation patterns in all 4 studies* | | | | |
| | | | | |
| *isolated immune cells: basophils & antiserum against IgE* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Davenas 1988 [32] | Benveniste 1991 [33] | | |
| *multicentre* | | | | |
| *external* | | | Ovelgönne 1992 [34] | |
| | | | Hirst 1993 [35] | |
| *resumee: reduction of degranulation in 2 studies, zero result in 2* | | | | |
| | | | | |
| *isolated immune cells: basophils & apis mellifica* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Poitevin 1986 [36] | Poitevin 1988 [37] | | |
| | | Benveniste 1991 [33] | | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: reduction of degranulation in all 3 studies* | | | | |
| | | | | |
| *isolated immune cells: basophils & histamine* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | St. Laudy 1991 [38] | St. Laudy 1993 [39] | | St. Laudy 2001 [50] |
| | | St. Laudy 1996 [40] | | |
| | | St. Laudy 1997 [41] | | |
| | | St. Laudy 2006 [42] | | |
| | | St. Laudy 2008 [43] | | |
| *multicentre* | | St. Laudy 2004 [44] | Wiegant 2004 [44] | |
| | | Ennis 2004 [44] | | |
| | | Mannaioni 2004 [44] | | |
| *external* | | Brown 2001 [45] | Guggisberg 2005 [48] | |
| | | Lorenz 2003 [46] | Wälchli 2012 [49] | Lorenz 2003 [51] |
| | | Chirumbolo 2009 [47] | | |
| *resumee: inhibition of degranulation in 13 studies, stimulation in 2, zero result in 3* | | | | |
| *hypthesis: different susceptibility of basophils from different donors* | | | | |
| | | | | |
| *isolated immune cells: lymphocytes & phytolacca americana* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Colas 1984 [52] | | | |
| *multicentre* | | | | |
| *external* | | | Bildet 1984 [53] | |
| *resumee: decrease of lymphocyte reaction in 1 study, zero result in 1* | | | | |
| | | | | |
| *isolated immune cells: lymphocytes & N-methyl-N'-nitro-N-nitrosoguanidine* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Francis 1990 [54] | | Anderson 1999 [55] | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: decrease of lymphocyte reaction in 1 study, zero result in 1* | | | | |
| | | | | |
| *isolated organs: rat intestine contraction & atropa belladonna or atropine sulfate* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Cristea 1997 [56] | | | |
| *multicentre* | | | | |
| *external* | | Schmidt 2004 [57] | | |
| | | Radau 2004 [58] | | |
| | | Michael 2004 [59] | | |
| *resumee: increase or decrease of contraction at different potency levels in all 4 studies* | | | | |
| | | | | |
| *animals: amphibian metamorphosis & thyroxin / thyroidinum / triiodothyronine* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Endler 1991 [60] | | Harrer 2014 [66] | |
| *multicentre* | | Pongratz 1991 [60] | Weber 2007 [62] | |
| | | van Wijk 1991 [60] | | |
| | | Zausner 2002 [61,98] | | |
| | | Pongratz 2002 [61] | | |
| | | Lassnig 2002 [61] | | |
| | | Welles 2007 [62] | | |
| | | Pongratz 2007 [62] | | |
| | | Suanjak 2007 [62] | | |
| *external* | | Guedes 2004 [63] | | |
| | | Guedes 2011 [64] | | |

*(Continued on next page)*

Table 1. *(Continued)*

| | | | | |
|---|---|---|---|---|
| | | Harrer 2012 [65] | | |
| *resumee: decrease of metamorphosis speed in 12 studies, zero result in 2* | | | | |
| *hypothesis: extreme precooling of animals in Harrer 2014* | | | | |
| | | | | |
| *animals: amphibian metamorphosis & thyroxin sealed in glass vials* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Endler 1994 [67,99] | | Dieterle 1998 [69,100] | |
| *multicentre* | | Waltl/Gehrer 1994 [67,99] | | |
| | | Pongratz 1994 [67,99] | | |
| | | Vinattieri 1995 [67,69] | | |
| | | Hilgers 1995 [67,69] | | |
| | | Hermann 2005 [68] | | |
| *external* | | | | |
| *resumee: decrease of metamorphosis speed in 6 studies, zero result in 1* | | | | |
| | | | | |
| *animals: frog climbing activity & thyroxin* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Endler 1991 [70] | | | |
| *multicentre* | | Pongratz 1994 [71] | | |
| *external* | | | | |
| *resumee: decrease of climbing activity in both studies* | | | | |
| | | | | |
| *animals: fish and homeopathic complex including iodine* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Junior 2012 [72] | Merlini 2014 [73] | Braccini 2013 [74] | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: decrease in gain of size and weight in 2 studies, zero result in 1* | | | | |
| | | | | |
| *animals: arsenic trioxide poisoned mice & arsenicum album* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Mitra 1998 [75] | Mitra 1999 [76] | | |
| | | Datta 1999 [77] | | |
| | | Kundu 2000 [78] | | |
| | | Mallick 2003 [79] | | |
| | | Banerjee 2007 [80] | | |
| | | Banerjee 2008 [81] | | |
| | | Banerjee 2009 [82] | | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: stimulation of damage repair in all 8 studies* | | | | |
| | | | | |
| *animals: mercury poisoned mice & mercury* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Larue 1985 [83] | Cal 1986 [84] | | |
| | | Larue 1986 [85] | | |
| | | Larue 1986 [86] | | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: protection effect in all 4 studies* | | | | |
| | | | | |
| *animals: carbon tetrachloride poisoned rats & phosphorus* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Bildet 1975 [87] | | | |
| *multicentre* | | | | |
| *external* | | Andresen 1985 [88] | | |
| *resumee: protection effect in both studies* | | | | |
| | | | | |
| *animals: lead poisoned rats & plumbum metallicum* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Fisher 1982 [89] | | Fisher 1987 [90] | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: incease of excretion in 1 study, zero effect in 1* | | | | |
| | | | | |
| *animals: thrombus formation in rats & acetyl salicylic acid* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Doutremepuich 1994 [91] | Belougne-Malfatti 1998 [92] | | |
| | | Aguejouf 2000 [93] | | |
| | | Eizayaga 2005 [94] | | |
| | | Doutremepuich 2007 [95] | | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: incease in thrombus formation in all 5 studies* | | | | |
| | | | | |
| *animals: mice under stress & gelsemium* | | | | |
| | *initial study* | *repet comparable* | *repet zero* | *repet opposite* |
| *initial lab* | Bellavite 2010 [96,101] | Bellavite 2011 [97] | | |
| *multicentre* | | | | |
| *external* | | | | |
| *resumee: improvement of behaviour in both studies* | | | | |

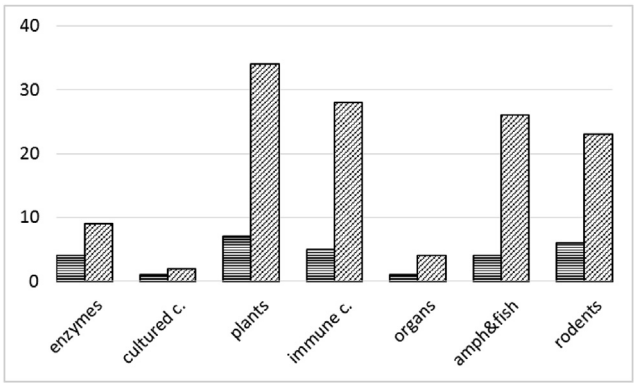


**Figure 1** Grouping of models and studies using ultra high dilutions on enzymes, cultured cells, plants, immune cells, isolated organs, amphibians/fish and rats/mice. Columns with horizontal lines: number of models submitted to replication; columns with diagonal lines: total number of studies, i.e. including both initial and replication studies.

The selected literature base comprised 101 publications (4 of which referred to one and the same study, giving additional details)[1–101] with data on a total of 126 *studies* (experiments), performed on a total of 28 experimental models. 28 of these were initial studies (on the 28 models) and 98 were replication studies. Of these replication studies, 41 were laboratory-internal replications, 28 multicentre replications and 29 external replications. Table 1 sums up the 28 models and classifies the identified 126 studies according to the type of replication and to results achieved. Multicentre studies were listed separately for the centres involved.

When all 98 replicative studies were considered, 70.4% (i.e. 69) reported a result comparable to that of the initial study, 20.4% (20) zero effect and 9.2% (9) an opposite result.

Figure 2 illustrates for the studies until 1994 (left) and the studies 1995–2015 (right) that the null-hypothesis, i.e. that there are no differences between the test and the control groups (dominance of zero results), should be rejected. Furthermore, the odds of finding a *comparable* result (white bars) are generally higher than of finding an *opposite* result (black bars). Although this is true for all three types of replication studies, it can be seen that the fraction of comparable studies diminishes from laboratory-internal (total 82.9%) to multicentre (total 75%) to external (total 48.3%).

When, for the total of the studies, the results on models that were only externally replicated (see Figure 3, left) and on models that were (mostly previous to the external replication) submitted to laboratory-internal or multicentre replication (Figure 3, right) were compared, it became obvious that the probability of an external replication producing opposite results is bigger for models that have not been further scrutinized by the initial researchers and that the probability of it producing a comparable result is bigger for models that have been submitted to laboratory-internal or multicentre replication.

## Discussion

Some general issues regarding methodology and the results of a first survey as well as desirable publication standards have been discussed previously.[102,114,115] Then, the

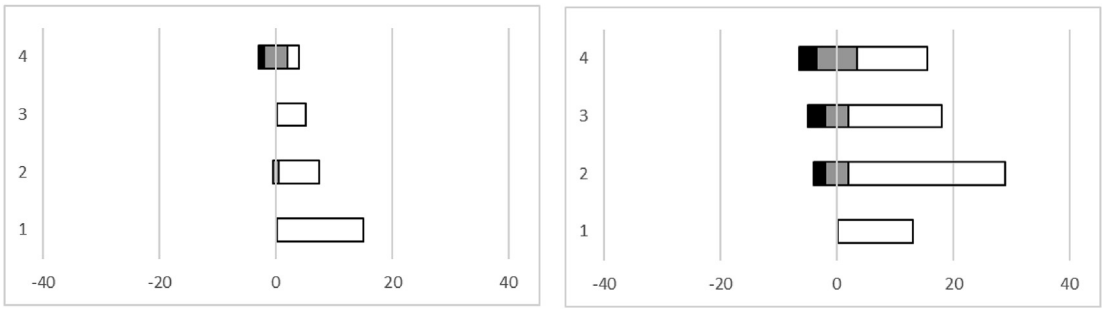


**Figure 2** Initial and replicated studies from Table 1. Left: studies until 1994; right: 1995–2015. Ordinate: 1: initial studies; 2: internal replications; 3: multicentre; 4: external replications. Abscissa: number of studies; -: opposite result. White bars 1 are identical with the number of initial studies; white bars 2–4: comparable results; grey bars 2–4: zero effect; black bars 2–4: opposite results.

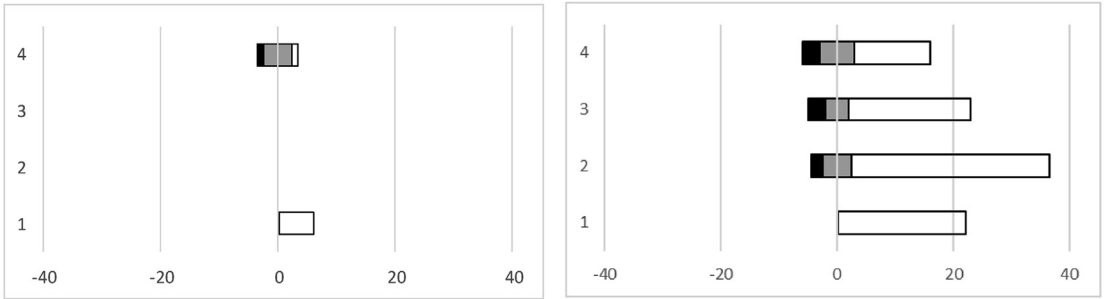


**Figure 3** Initial and replicated studies from Table 1. Left: studies that were only externally replicated; right: models that were submitted to laboratory-internal or multicentre replication. For further explanation, see Figure 2.

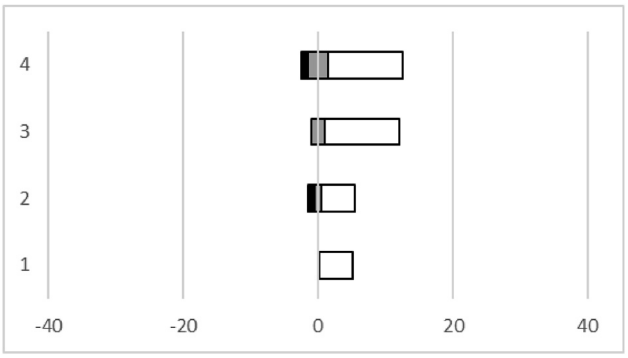


**Figure 4** Initial and replicated studies for models that have been externally reproduced with comparable results. For further explanation, see Figure 2.

point of departure in attempting an assessment of the results was one of the paradigms of homeopathy, namely that the primary aim of an homeopathic intervention is to dislodge the organism being treated from its stuck, pathological state, regardless of the direction the change may take. This paradigm finds support in clinical reports according to which healing often first manifests itself as an initial aggravation. It also finds support in zoological experiments where it seemed to be possible to steer decrease or increase of metamorphosis speed in amphibians by alternating the time interval between administration of a potentized test substance's dose.[99,pp54–58] Indeterminacy of effect direction has been found in certain plant studies with their mutually opposite, yet in either case homogeneous, statistically significant results.[22,24,116] The following two working hypotheses were initially considered but then found to be unsuitable for evaluating the present bibliometric data: that studies in favour of homeopathy would lead to *comparable or opposite* results (tested *versus* zero results), because this could lead to false-positive conclusions; or that studies in favour of a sceptic viewpoint would lead to *opposite or zero* results (tested *versus* comparable results), as this could lead to false-negative conclusions.

Instead, the null-hypothesis adopted was that test and control groups would not be distinguishable, i.e. there would be no result of treatment with the potency. Based on a graphic representation of the results it would then be possible to compare the odds for the occurrence of comparable results and opposite results.

Irreproducibility of results can be due to the fact that the results of the initial studies were artefacts (i.e. false-positive results). Artefacts can be due to contamination, systematic drifts or stochastic noise of the experimental set-up, which are wrongly interpreted as treatment results. Furthermore, the same reasons that can lead to result inversions may also lead to zero effects: uncontrolled relevant parameters, inappropriate outcome measures, or system inherent irreproducibility. A detailed discussion of these possible reasons for problems with reproducibility can be found elsewhere.[117] In some cases the laboratory know-how may not have been communicated in sufficient detail. This can be obviated by organising a training phase in the initial laboratory before an attempt is made to repeat a study. On going through the list of researchers whose replication research has at times produced zero effects one will incidentally also come across ones who can absolutely be counted among the homeopathy research community (Table 1). Another example is one external researcher who first found a comparable effect[65] and then, after joining the initial laboratory's team and, after changing a crucial laboratory parameter for exploratory purposes (i.e. temperature), a zero effect.[66]

## External repetitions

External replication studies yielded 48.3% comparable, 37.9% zero, and 13.8% opposite results.

We identified five models that have been reproduced by at least one external research team with comparable results:

1. Growth of wheat seedlings after treatment with potencies of silver nitrate,[13–15]
2. Human basophil degranulation after treatment with potencies of histamine,[38–51]
3. Highland amphibian metamorphosis after treatment with potencies of thyroxin or thyroidinum,[60–66,98]
4. Contraction of rat intestine *in vitro* after treatment with potencies of atropa belladonna or atropine sulphate,[56–59]
5. Experimental hepatitis of the rat due to poisoning with carbon tetrachloride after treatment with phosphorus.[87,89]

Minor methodological differences between these replication studies and the initial studies preceding them have been critically discussed.[102] While every effort was made to group the literature under survey into meaningful clusters, it is obvious that ours was not the only plausible choice and that one could find arguments in favour of other solutions. Recent studies on histological changes in cut-off tails of non-highland amphibians *Rana catesbeiana*[63,64] were grouped together with whole organism studies on highland amphibians *Rana temporaria*[60–62,65,66] mainly in view of the fact that both models deal with the effects of highly diluted thyroid hormones on a certain period in metamorphosis. On the other hand, some clusters could have been made even broader: For example, the cluster on the basophil model[39–51] involving potentized histamine could have been extended to include studies on high dilutions of adrenaline[118]; or one could have created a cluster out of all studies dealing with the effects of high dilutions on DNA expression, which has been implied by studies on different systems in different laboratories[119]; or a cluster comprising studies on the anxiolytic effects of highly diluted *Gelsemium* not only on mice,[96,97,102] but also other animals[120–122] as well as neurocytes *in vitro*, suggesting decreased cell excitability.[123,124] Furthermore, '>23x' may be too strict considering that in the homeopathic production process a mother tincture, depending on the pharmacopoeia used, may occasionally contain only $10^{-3}$, $10^{-4}$ or $10^{-5}$ moles of the original substance per litre, i.e. their 23-fold dilution 1:10 will lead to 26x, 27x or 28x. This may be especially relevant

for the inclusion of some models by Bastide *et al.* who used 20x potencies.[125]

### The multicentre approach

When all replication (i.e. excluding the initial) studies are considered, 70.4% report a result comparable to that of the initial study, 20.4% a zero effect and 9.2% an opposite result. This relation is fairly well reflected by multicentre studies, i.e. studies that were centrally organised, but carried out by various researchers in different laboratories, namely 75% comparable, 14.3% zero and 10.7% opposite results. Thus, multicentre studies seem to be an adequate tool for investigating fundamental high potency models.

### Laboratory-internal replication

On the other hand, initial researcher or working group studies show 82.9% comparable, 12.2% zero and 4.8% opposite results. This outcome may partly be attributable to methodological details not made explicit in the publications.

### Assessing the potential of experimental models

When replication trials consistently yield zero effects one will sooner or later consider abandoning the model in question. On the other hand, when replication trials have yielded non-comparable results only in isolated cases it will make sense to review the entirety of studies published on that model before one decides to turn away from what might otherwise still grow into a fruitful branch of research.

When we screened our study material for links between the outcome of external replication studies and the history of laboratory-internal and multicentre replication work on the same model we found that initial studies that had not been followed up with laboratory-internal or multicentre replications were more likely to lead to zero effects on external replication than when they had. It thus appears that internal or multicentre replication studies, along with publications detailing the methods used and results obtained, are worth the effort if one wants to increase the probability of external researchers obtaining comparable results. On the other hand one must consider the possibility that a zero effect found on internal replication will discourage attempts at external replication.

Figure 4 shows the outcomes of the 40 studies covering the 5 models that were externally replicated with comparable results. It can be seen that some of these studies also produced zero effects or opposite results.

### 1994 and 2015

Furthermore, the state of replication two decades ago, i.e. in 1994,[99] was compared with that in 2015. Of the 28 models on which there had been replication work up until 2015, 15 had replication studies published before or in 1994, including 4 of the 5 promising models mentioned above. Of these 5 models, two underwent external replication before or in 1994 (Kolisko[13] repeated by Scherer-Pongratz[14]; Bildet[87] repeated by Andresen[88]) and three after 1994 (St. Laudy,[38–51] Cristea,[56–59] Endler[60–66]).

## Conclusion

We found 28 experimental models in basic research on high homeopathic potencies which underwent replication research. *In total*, 24 models were replicated with comparable results, 12 models with zero effect, and 6 models with opposite results. Five models were *externally* reproduced with comparable results.

We strongly encourage further replications of published studies in order to learn more about the model systems used, to identify crucial parameters influencing experimental outcome, and to test repeatability of results. For this purpose the research methods, as well as the presentation of methods and results, should meet certain minimum standards, e.g. the guidelines for studies in homeopathy,[98,99] either in the publication itself or in a readily available background website. As in other fields of science, a training phase in the initial laboratory may be recommendable before one attempts to repeat a study.

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### Annotation

The authors will be grateful for comments and further information on relevant studies that fit the inclusion criteria of the bibliography. It may be of interest to the research community to further refine this publication from an annotated bibliography into a fully detailed review. It may also be of interest to use the bibliographic assessment standardized here in other fields of research, e.g. with regard to clinical trials on homeopathy.

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