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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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2009¹⁰² 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 publication¹⁰² 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. $\geq 24x$ ($=10^{-24}$) 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/labora-

tories, 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 1994¹⁰² 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 & ubiquinone				
	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 H2O2 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	Walchli 2012 ⁴⁸	Lorenz 2003 ⁵¹
		Chirumbolo 2009 ⁴⁷		
resumee: inhibition of degranulation in 13 studies, stimulation in 2, zero result in 3				
hypothesis: 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 ^{61,68}		
		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 ^{67,69}		Dieterle 1998 ^{68,100}	
multicentre		Walt/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: increase 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		
		Aguejof 2000 ⁹³		
		Eizayaga 2005 ⁹⁴		
		Doutremepuich 2007 ⁹⁵		
multicentre				
external				
resumee: increase 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				

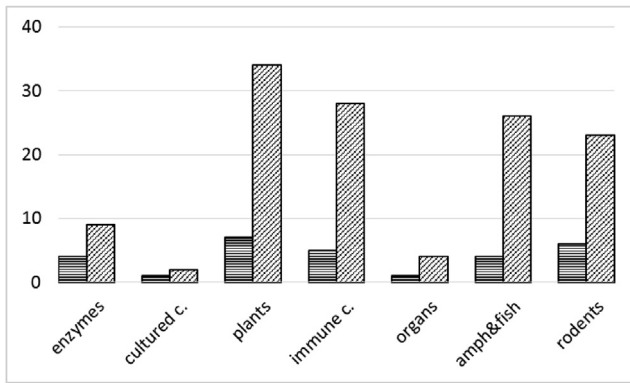


Figure 1 Grouping of models and studies using ultra high dilutions on enzymes, cultured cells, plants, immune cells, isolated organs, amphibians/fish and rats/mice. Columns with horizontal lines: number of models submitted to replication; columns with diagonal lines: total number of studies, i.e. including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

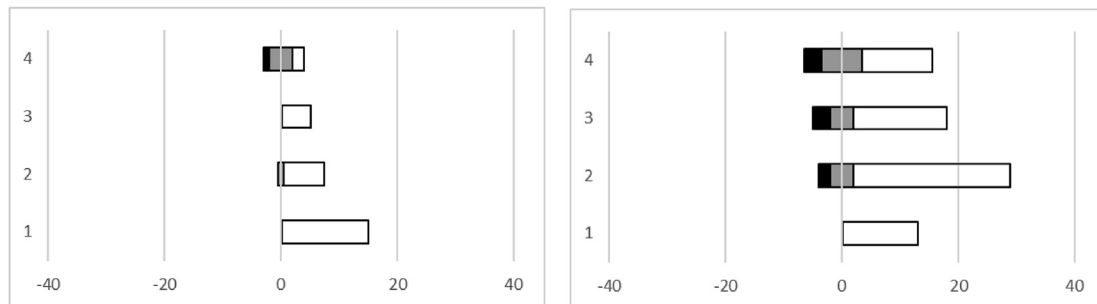


Figure 2 Initial and replicated studies from Table 1. Left: studies until 1994; right: 1995–2015. Ordinate: 1: initial studies; 2: internal replications; 3: multicentre; 4: external replications. Abscissa: number of studies; -: opposite result. White bars 1 are identical with the number of initial studies;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

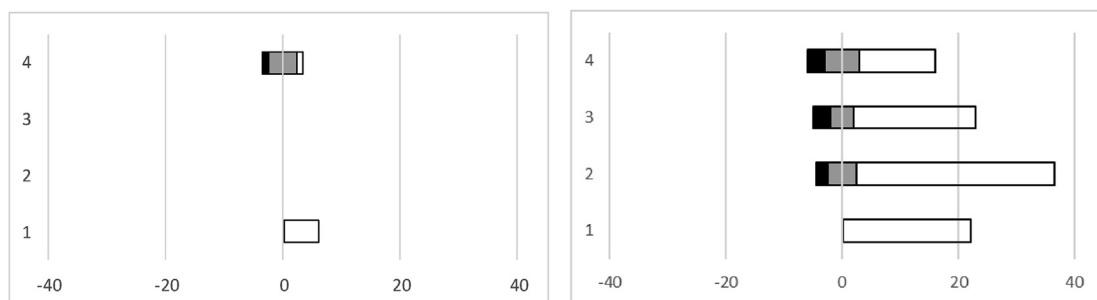


Figure 3 Initial and replicated studies from Table 1. Left: studies that were only externally replicated; right: models that were submitted to laboratory-internal or multicentre replication. For further explanation, see Figure 2.

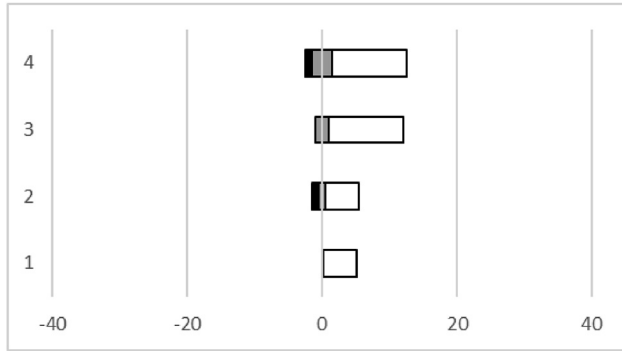


Figure 4 Initial and replicated studies for models that have been externally reproduced with comparable results. For further explanation, see Figure 2.

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 effect⁶⁵ 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 thyroxine 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 adrenaline¹¹⁸; 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 laboratories¹¹⁹; 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 (Kolisko¹³ repeated by Scherer-Pon-

gratz¹⁴; Bildet⁸⁷ repeated by Andresen⁸⁸) 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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